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**ROYAL COMMISSION OF INQUIRY INTO CERTAIN
DEATHS AT THE HOSPITAL FOR SICK CHILDREN AND
RELATED MATTERS.**

Hearing held in Court Room 20
Court House
361 University Avenue
Toronto, Ontario

The Honourable Mr. Justice S.G.M. Grange

Commissioner

P.S.A. Lamek, Q.C.

Counsel

E.A. Cronk

Associate Counsel

Thomas Millar

Administrator

Transcript of evidence
for

June 28th, 1983

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1983.

THE HONOURABLE MR. JUSTICE S.G.M. GRANGE - Commissioner
THOMAS MILLAR - Administrator
MURRAY R. ELLIOTT - Registrar

APPEARANCES:

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	Sick Children
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	Sick Children
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	Mr. & Mrs. Gionas, Mr. & Mrs.
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	Mr. & Mrs. Lutes (parents of
	deceased children)
F.J. AHANAHAN	Counsel for Mr. & Mrs. Dominic
	Lombardo (parents of deceased
	child Stephanie Lombardo)
W.T. TOBIAS	Counsel for Mr. & Mrs. Hines
	(parents of deceased child
	Jordan Hines)

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---Upon commencing at 11:30 a.m.

THE COMMISSIONER: Mr. Lamek.

MR. LAMEK: Mr. Commissioner, first of all I apologize to you and to other counsel and everybody else here for the late start this morning, it really was unavoidable. Dr. Mirkin was coming in from Minneapolis last night and the wonders of modern science overtook him, the aircraft were delayed and he did not arrive here until very late, and it was necessary to spend some time with him this morning and I apologize for that.

As I said last week, sir, I propose because Dr. Mirkin is only available today to lead his evidence in chief today and to ask him to come back for any cross-examination that counsel may have of him at a later date, I haven't been able to arrive at a date with him yet but I will let other counsel know that just as soon as I can.

I should say too, sir, that Dr. Mirkin's evidence today will be general evidence as to the drug digoxin. I hope he will appear on a later occasion to give his expert opinion evidence as to the particular assay results found in samples taken from particular children whose deaths are under review here, but that is not his purpose here today, sir.



1
2 May I call please, Dr. Bernard
3 Mirkin.

4 DR. BERNARD L. MIRKIN, Sworn

5 DIRECT-EXAMINATION BY MR. LAMEK:

6 Q. Dr. Mirkin, one of the most
7 embarrassing things about being called as an expert
8 witness is you have to sit and have someone put to
9 you your accomplishments and attainments, and I
10 don't propose to embarrass you to any great extent
11 with this. You have provided me with a copy of your
12 Curriculum Vitae listing the positions you have held
13 and the degrees that you hold and publications that
14 bear your name and several appointments that you
15 have received.

16 I wonder, Mr. Commissioner, if that
17 might be marked as the next exhibit?

18 ---EXHIBIT NO. 5: Curriculum Vitae - Dr. Bernard
19 L. Mirkin.

20 MR. LAMEK: Q. I can't spare you
21 completely, Dr. Mirkin. Let me just touch upon
22 one or two of the high points. You received your
23 Bachelor's degree from ^{New}York University in 1949?
24

25 A. Yes, that's correct.

Q. And a PhD from Yale in 1953?

A. Correct.



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Q. Could you tell us please, the
area of work for your PhD?

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A. In the work I performed, it
was in the area of pharmacology, basically pharma-
cology, the study of drugs and their effects in
living tissue.

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Q. And 11 years later in 1964 you
were graduated with a Degree of Doctor of Medicine
from the University of Minnesota, College of Medicine.

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A. That is correct.

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Q. And have held numerous positions
at the State University at New York and latterly
at the University of Minnesota where you are now,
as I understand it, the Director of the Division of
Pediatrics and Pharmacology; I'm sorry, Clinical
Pharmacology, and Professor of Pediatrics and
Pharmacology in the Medical School I take it?

22

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A. Correct.

Q. In 1973 you were a Visiting
Professor at Oxford and were appointed a Senior
Fellow of Jesus College working at the Nuffield
Institute for Medical Research I understand.

A. Yes.

Q. And in the following year, 1974,
was that the second half of the sabbatical year,

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you were at Cornell?

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A. No, I did a visiting professorship there for a brief period of time.

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Q. Visiting Professor at Cornell, at the University Medical College Department of Pediatrics and Pharmacology. Now, the list of your publications is contained in the Curriculum Vitae and I won't take the time to refer to any of them. You have written on many aspects of pharmacology and on many drugs including the one with which we are concerned, digoxin, is that a fair summary of a long publication history?

13

A. Yes, with due modesty.

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Q. Thank you, Doctor. Doctor, you have just defined for us almost in passing what pharmacology is. Could you tell us what is a clinical pharmacologist?

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A. A clinical pharmacologist is defined in many ways, but I have always felt it was ~~in~~ an individual who was attempting to apply basic understanding of the drugs in a setting where human disease is present. So that individuals who are clinical pharmacologists may not only be trained in basic pharmacology but are also considered to be skilled clinicians, and this is an area where



1
2 synthesis of basic knowledge occurs and applications
3 of these principles to therapeutic management of
4 patients is engaged in.

5 Q. I said, Doctor, we are concerned
6 here with a particular drug digoxin and I take it
7 that is a drug with which you have had some contact
8 in a clinical context.

9 A. That is correct.

10 Q. And in a research context?

11 A. Yes.

12 Q. As I see from the Curriculum
13 Vitae.

14 A. Yes.

15 Q. Can you tell me, Doctor, what
16 is digoxin?

17 A. Digoxin is a drug that was
18 originally used, oh, some 200 to 250 years ago and
19 it is derived from a very interesting flower. I
20 brought a picture for you to see and perhaps it will
21 be of some interest to flashes on the screen.

22 Q. Doctor, I should say we haven't
23 had time for me to see any of these things so they
24 are coming as a surprise to me. Perhaps if you could
25 come down here you could use that microphone if you
will just switch it on.



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A. Can you hear me?

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Q. I wonder if we could put on
this projector?

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A. Thank you. I hope I don't
make you do that too frequently. Unfortunately
I did not have a coloured photograph to place on
here, but this is the general flower and it grows
wild; digitalis lanatum and these petals are white. The
active product for those of you ^{who} are interested
derives not so much from the petals but perhaps from
some of the leaves and they are on the stem. I
have taken the liberty of bringing some of that
for you, those of you who would like to see it
during the recess, in an envelope, and green leaf.

15

16

17

There is also in the powder that is
used to make up tablets, sugar, and this is a rather
complicated process making up the tablets and we get
into that a bit later.

18

19

20

The drug itself consists of a rather
complex chemical structure and I thought I might take
the liberty to show you that quite quickly.

21

22

23

Q. If I may sit down
while you are doing that and I will be out of the
way and people can see what you are showing.

24

25

A. The drug actually was first



1
2 described, the use of this drug, foxglove I think is
3 its general name, and it was used by William
4 Withering round about 1700.

5 The drug is quite interesting because
6 even at that time, 1785 when it was actually written,
7 used by a Shropshire lady, and in 1785 Withering
8 wrote about this which is quite interesting.

9 Phrase One says:

10 "Let the medicine be continued
11 after it either acts on the kidneys,
12 the stomach, the pulse or the bowels
13 and let it be stopped upon the first
14 appearance of any of these effects."

15 It is quite intriguing that most
16 contemporary pharmacologists and cardiologists will
17 still find this to be a very acceptable classifica-
18 tion of the drug action.

19 The second part of course it has a
20 motion on the heart to a degree yet unobserved in
21 any medicine and that still holds true to this day.

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Now, the compound. At the time Dr. Withering was using it clinically, of course it did not pass the FDA, and we, in recent times, have been able to characterize this. I want to take the liberty of showing you this quite quickly.

The middle portion is the compound that we are going to be discussing today, digoxin. That is the chemical. You can see that it consists of three basic entities. The steroid which you can see up hereon Panel A, this is the so-called steroid nucleus. The steroid nucleus is common to all of the hormones in the human body, all have this as a basic component. So you see digitalis in a sense mimics some aspects of the human hormones. In addition, digitalis has this area here which is a lactone ring and down here this long C-18 chain, which is comprised of a sugar. So you have a sugar, you have the steroid nucleus and this lactone ring. That is really what digitalis is, or digoxin, and there are a variety of modifications of this, digitoxin, ouabain et cetera.

But our concern today is to be dealing with digoxin. I am hoping you remember this as we get into the testimony a bit later because this configuration, the steroid configuration, seems



1
2 to lead some problems in the assay of this compound.
3 There will be lots of discussion about the relative
4 merits and selectivity of assay procedures, but
5 presumably one of the reasons for this difficulty in
6 discrimination is the similarity of the steroid
7 nucleus in the digoxin with other compounds naturally
8 occurring in the body.

9 Q Dr. Mirkin, part of that message
10 is that digoxin or some form or version of digoxin
11 has been known to have some active biological effect
12 for some considerable time.

13 Can you tell me, please, in modern
14 medicine, and indeed it may not have changed, for
15 what conditions is the use of the drug indicated?

16 A Most frequently the drug is
17 used to treat patients with what is clinically
18 described as congestive heart failure or, in lay
19 terms, heart failure. That is a condition where
20 the heart muscle is, for one reason or another,
21 not effectively pumping blood throughout the body.
22 Essentially this is described as a failing heart,
23 and digoxin has the capacity to improve the function
24 of the muscle of the heart.

25 Q I noticed before we came into
Court today that you were referring to digoxin and



1
2 digitalis almost interchangeably. What is the
3 distinction, if any, between those two?

4 A. I think it is historical and
5 generic in the sense that digitalis was formerly
6 used in the form of a tincture. There may be
7 some old enough in this room to recall its use in
8 that form. It is still currently prescribed in
9 that form in some locales.

10 What this meant was that the leaf
11 I alluded to earlier was ground up and essentially
12 extracted in alcohol and perhaps some water - I
13 think mostly alcohol. What this led to was a
14 solution of varying strengths. It could not be
15 standardized. So that is generally what we are
16 referring to when we call digitalis, tincture of
17 digitalis is one way in which this is dispensed.

18 When it became apparent that the
19 digitalis leaf contained not only so-called digitalis—
20 digitalis was a composition or composite of a
21 variety of different materials, digitoxin, ouabain
22 and digoxin and perhaps other glycosides— the
23 effort was made to purify this and use a discrete
24 chemical entity, so digoxin was able to be extracted
25 and standardized so when a dose is given to a patient
one knows the precise amount of a chemical substance



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that is being administered.

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In practice, digitoxin is used clinically extensively, digoxin or Lanovin, as the trade name, I think that is what the trade name is in Canada, and also another compound ouabain. These are the three major glycosides which are used in contemporary clinical practice.

Q. Can you tell me, please, what is the action of digoxin when administered? You told me the condition for which it is primarily used, that of congestive heart failure. How does digoxin deal with that situation? How does it assist it?

A. The primary function of digoxin is to improve the efficiency with which the myocardium, that is, the heart muscle, contracts. As I mentioned previously the major problem in a patient with heart failure is that this pump, the thorax, is not effectively circulating or pumping blood throughout the body. This leads to a large number of unpleasant and non-physiologic circumstances in the patient. Digoxin, when it is given, improves the efficiency with which the muscle can contract. The mechanisms whereby this is accomplished are still somewhat obscure but,



1
2 as you might imagine in 250 years, there has been
3 a lot of research but, like with most research,
4 rather slight enlightenment occurs sometimes.

5 But I think it is fair to say the
6 current feeling is that digoxin affects an enzyme
7 system called sodium potassium A T Pase system which
8 plays an integral role in the contraction of
9 myocardial and perhaps skeletal muscle and by so
10 influencing this enzyme system digoxin enhances
11 the capacity of the failing heart to more effectively
12 pump blood through the body.

13 Q. That was its primary effect.
14 Is there any other effect?
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2 **A.** Well, as you recognize, drugs are not
3 as specific as we like to make them out.

4 Erlich or Pasteur's
5 magic bullet was not as magic or as specific as
6 it seemed to be. Most drugs affect a wide variety
7 of systems and structures in the body. In fact,
8 it is safe to say that drugs act, they have a sort
9 of ubiquitous activity.

10 Now, digitalis is no different. Its
11 primary effect, of course, is to increase the
12 efficiency with which the heart muscle contracts
13 and, therefore, this leads to increased force of
14 contraction, greater efficiency in pushing blood
15 around through the circulatory system in the body.

16 Another affect that is associated
17 with this is the influence of digitalis on the
18 specialized conducting system of the heart.

19 Now, if I may diverge just a bit. The
20 heart has an internal intrinsic system that allows
21 an impulse to go from one chamber to the other.
22 I was trying to describe that earlier in the day,
23 maybe I can stand up and show this to you. This
24 is the atrium of the heart. That is essentially --
25 the heart has four chambers and the smaller chambers,
the left and right atrium are here. This is the



1
2 ventricular, which are the left and right ventricles,
3 which are really the pumping stations for the heart.

4 Connecting the two, my thumbs, are
5 a sequence of networks that are not dissimilar to
6 telephone wires. So that an impulse arising
7 in the atrium is carried through this network, so-
8 called atrial ventricular node, which is the name
9 given to it, to the ventricular, and this impulse
10 beats here. So, the normal sequence would be the
11 sequence of this sort of beat in the atrium going
12 through this pathway and contractions in the
ventricular.

13 It is here now that digoxin not only
14 acts to increase the force of contractions, but has
15 an effect on conduction so that the impulses at
16 certain concentrations are impeded; that is,
17 the rate of conduction down this pathway is
slow.

18 As a consequence of this, too much
19 digoxin leads to a dissociation of the beats in
20 the atrium and the ventricular. You have what is
21 called atrial ventricular dissociation, and that's
22 a very, very dangerous situation where the ventricular
23 is beating on its own at a very slow rate; and too
24 much digoxin, too much, will lead to a state where
25



1
2 the heart essentially stops beating in a state of
3 sustained and intense contraction.

4 So, then, let me recapitulate. You
5 have the positive therapeutic effect of the drug,
6 it's increasing the contraction of and the
7 efficiency of contraction of the muscle, ~~You~~ have
8 a situation ^{where} ~~with~~ too much digoxin can cause a
9 sustained and unrelenting contraction with loss of
10 function. You have a situation where the conduction
11 from one portion of the heart to the other portion
12 of the heart may be impeded by too much digoxin.

13 I think those characteristics of the
14 effects of the drug probably are the ones that
15 are the major ones and from which we can really
16 adduce any other effects that are observed with
17 this drug.

18 Q. Doctor, you referred to atrial
19 ventricular dissociation, if there is too
20 much digoxin at work, and you have described
21 that as a very, very dangerous situation. At
22 levels which are commonly regarded as therapeutic
23 and I want to come back to just what that means
24 later, but at levels that are commonly regarded
25 as therapeutic, is there nevertheless some element of



1
2 this blocking or slowing down of the impulse through
3 the atrial ventricular node.

4 A. Well, to specifically answer
5 that question. We are getting into the realm of
6 how does digoxin exert its beneficial effects.
7 What's the consequence of improving the contraction
8 of the heart, is this good or bad for the patient
9 and what sequelae emerge from it. Obviously,
10 if we have a failing heart it stands to reason
11 that improving the efficiency of the contraction
12 will generally have a beneficial effect on the
13 patient.

14 The way this occurs is that in a
15 patient with a failing heart, the amount of blood
16 that is pumped out by the heart per unit time, that
17 is, the so-called cardiac output, the amount of
18 blood pumped out is reduced.

19 For each beat of the heart a smaller
20 amount of blood is pumped out than occurs in a
21 normal individual. The heart makes up for this
22 by increasing its rate.

23 If you have a smaller amount coming
24 out per beat, you increase the rate you have,
25 over a given time equal perhaps what a normal heart



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can achieve at a slower rate.

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You've probably read about marathon runners who have heartrates of 40 after running 21 miles -- not quite mine -- but that is how that is achieved, because the well conditioned individual can pump large amounts of blood each beat. The person in a failing heart pumps a small amount of blood and to compensate for this must have a more rapid heart rate.

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So, the patient in failure will have these characteristics.

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Now, digoxin, by improving the force of contraction, allows not only more blood to be pumped per unit per beat, but improves the general adaptation of the body to this condition so that once the body recognizes that the heart is putting out a large amount of blood per beat, it slows down the rate of the heart. So, you have a reciprocal system.

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The way this is achieved is by nervous structures in the body that receive this signal and send signals to the brain which then sends a signal down to the heart to slow down its rate. This is achieved through a nerve called the



1
2 vagus nerve and the vagus nerve has a profound
3 effect on the intrinsic heart rate through its
4 action on the sinoatrial node, the SA node, which
5 is located in the small chamber, the atrium. Is
6 that it?

7 Q. Yes, I think that helps us,
8 Doctor.

9 So that if I understand you correctly,
10 the reduced heart rate is a result of the strengthened
11 and more efficient contractions of the heart.

12 A. Exactly. It is a compensatory
13 response of the body to the improved condition of
14 its circulation.

15 Q. Now, you have told us of the
16 primary condition for which the use of digoxin is
17 indicated. Is there any condition~~s~~ for which
18 its use is -- I believe the term is contra-indicated?
19 It's not a lawyer's term and it doesn't trip easily
20 from my mouth.

21 A. Well, I think one could define
22 the circumstances where digoxin should not be used.
23 Now, I'm not quite certain whether you are
24 alluding to specific cardiac disease states.

25 Q. Yes, I am interested in cardiac



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states, yes.

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A. Yes. Well, I think that

certainly in some individuals where there are well

defined rhythm disturbances, it is questionable

whether digoxin should be given. For example, when

individuals have abnormalities in their ventricular

rate, where they have ventricular tachycardia, for

example, no one should give digitalis because this

will exacerbate the condition.

Q. I'm sorry, Doctor, I have to

interrupt you. Tachycardia means fast heart rate?

A. Very fast heart rate. That

is where the ventricular per se is beating very

rapidly. Now, this gets to be a bit complicated.

There are a variety of conditions which can cause

a rapid heart rate.



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One of these conditions is a situation where the atrium is beating very rapidly and this is called atrial ~~fibulation~~ ^{fibrillation} or atrial flutter. In this case digitalis is used in an effort to slow down the rate of conduction of impulses to the ventricular, and the net clinical effect is to result in a slowing of ventricular rate. I hope that point is clear, it is not responsive to the question you asked because you asked what condition should we not use it.

Q. Yes.

A. I am a little hard pressed to answer that clearly now and maybe I can defer that for a moment.

Q. Okay. You have identified ventricular tachycardia.

A. Ventricular tachycardia is a distinct case where it should not be used. It probably should not be used, or used with caution, certainly in patients who are known to have significant electrolyte deficiencies. That is something we can get into later.

Q. I am sorry, can you just define electrolyte for us.



1
2 A. It should be used with caution
3 in patients who are in situations where the potassium
4 level in the blood and/or tissues is very low. Also
5 one might argue that where the calcium level is very
6 high it should be used with caution, though it can
7 certainly be used in those conditions.

8 We will define some specific cardio-
9 vascular conditions where it probably is contraindicated
10 a bit later.

11 Q. And how in a clinical setting is
12 the drug administered, Doctor?

13 A. The normal routes of administra-
14 tion are oral and parenteral, and by the latter I
15 include intramuscular and intravenous routes of
16 administration.

17 Q. Parenteral meaning essentially
18 what, through the wall of the body?

19 A. Yes. Not through the alimentary
20 canal. I do have a reprint, a German reprint in which
21 the drug was given as a suppository in an alleged
22 murder case which might be fascinating reading for
23 historians here.

24 Q. Or German reading historians,
25 anyway.



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A. Well, I thought everyone was bilingual here.

Q. All right, then, Doctor, once we have identified a situation which calls for the administration of digoxin and the drug has been administered, either orally or as I say intravenously, can you tell us please what happens to the drug immediately after administration, and what does it do, where does it go, where does it accumulate and how does it do whatever it does?

A. Well, let me get back to the drawing board on this for a minute. I tried to make some of these diagrams as clearly as I could, so if there are any questions, please don't hesitate to interrupt me. There are two possibilities, or probably more than two. One situation occurs when the drug is given orally and this is the most common route of administration in patients who are not acutely ill, or who are too moribund to take the drug.

When the drug is given orally, and this is digoxin, it comes through the esophagus and gets into the intestines, you can see it through here. In the intestines we have absorption of the



1
2 drug. Any drug that is absorbed from the intestines
3 must go through a very specialized segment of the
4 circulation called the portal system. Now, the
5 portal system is simply a mechanism that allows
6 the drug to go from the intestines, as you see
7 this arrow, back into the liver, this is essentially
8 the portal system (indicating). It is a specialized
9 series of blood vessels that feed into the liver.
10 So, consequently a drug, any drug that is given
11 orally must have this pathway. From the liver a
12 certain amount of the drug may be found in the liver,
13 a certain amount of the drug may be metabolized
14 in the liver. But in this particular case, with
15 digoxin, very little is metabolized. Virtually
16 not for practical purposes, but we will say 95%
17 is non-metabolized and 5% possibly metabolized,
18 we can use those figures for our dialogue today.

19 The drug, once it gets into the liver,
20 that part which is not bound to the liver then
21 returns to the systemic, to the general circulation
22 and once it enters the general circulation, not
23 shown on this diagram, it then can be distributed to
24 other tissues and organs in the body.

25 I point this out merely to illustrate



1
2 the rather circumventuous path that an oral dose
3 takes before it gets into the bloodstream. This,
4 of course, is with all drugs, and this traversing
5 through the intestine and the liver results in
6 the fact that you have a blood level peak that
7 occurs one to two hours after ingestion of digoxin,
8 in this case, and it varies with other drugs.

9 You can see that the peak level is
10 going to be influenced by a lot of other things.
11 You might have a circumstance where a very active
12 duct, hypomotility, you may have an ulcer and I
13 am sure I am covering, with that category, 85% of
14 the people in the room, or perhaps you may be
15 constipated and that makes it 100%. All of these
16 factors influence the absorption of the drug in
17 an individual.

18 As a matter of fact, cathartics and
19 other things that patients use can also influence
20 the absorption of the drug. I think the crucial
21 thing is there is a temporal lag between the
22 administration of the drug and the development of
23 the maximum blood levels.

24 To give you an idea of the distinction,
25 or at least a clear distinction that can be made



1
2 between the oral route -- can you all see this?
3 In the upper left you see the pattern here, the
4 patient is given the drug and about one to two
5 hours after administration it goes down, this is
6 a single dose.

7 When the drug is given intravenously,
8 this is now the parenteral route of administration,
9 we have as you know a very rapid onset of relatively
10 high concentration.

11 There are two points I just want to
12 illustrate about these diagrams. One is when we
13 use the drug orally, you can see for this illustration
14 at least that the concentration achieved is probably
15 lower than when an equivalent amount is given
16 intravenously. Okay. The reason for this is
17 with the intravenous route you have the entire
18 drug concentration, there is no loss, all going into
19 the bloodstream, so 100% of the drug is being
20 delivered, this gets into the concept of bio-
21 availability which I presume has been discussed and
22 we will go into that a bit later.

23 You can see that obviously if we
24 use the same amount here in the oral as we used
25 in the intravenous administration, there must be



1
2 some material that was either lost or the rate of
3 absorption essentially occurs at such a pace that
4 the rate of absorption may not be equivalent to
5 the rate of elimination.

6 Now, the point there, the drug
7 digoxin is eliminated by the kidneys, primarily,
8 and you must be aware that patients who have poor
9 renal function eliminate the drug more slowly and
10 we can get into that a bit later. I just want to
11 illustrate here the distinction between the oral
12 on the left and the intravenous on the right.

13 Q. Doctor, could I just be clear
14 about a couple of things.

15 A. Sure.

16 Q. First, while you have this
17 transparency on the screen, you are referring at
18 this stage only to levels in the circulatory system.

19 A. That is correct.

20 Q. And that is what the graphs
21 are showing. As I understand it, the circulatory
22 system really acts as a delivery system delivering
23 the drug to the various organs and tissues in the
24 body.

25 A. That is correct.



1
2 Q. Now, in terms of the apparently
3 lower levels in the circulatory system that are achieved
4 after a couple of hours after an oral dose of
5 digoxin, as compared with an intravenous dose of
6 digoxin, is part of the explanation for that
7 apparent loss is that the absorption is taking place
8 into the bloodstream over a longer period of time,
9 and therefore the total amount of digoxin absorbed
10 into the circulatory system, even by oral administra-
11 tion, may be very close to that which is delivered
12 directly to the circulatory system by injection?

13 A. Yes, that is a very precise
14 analysis, I can't improve on it. That is perfectly
15 correct. The only addition I could make, the only
16 addition I would make is that a way of measuring
17 what Mr. Lamek has just described is like taking
18 the area, if you look under these curves there is
19 an area. Can you see it? And one can integrate
20 this area. The area under this curve and the
21 flat area under this curve, although they look some-
22 what different, you will find they are very close
23 to one another, and that is a reflection of the total
24 amount of the drug. Essentially what he said was
25 that the absorption of this drug and the bioavailability



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2 of it is excellent, so that 85%, sometimes 90%
3 of a given dose can be assumed, based on
4 experimental data, to have been received by the
5 individual's circulatory system, that is very
6 high when we compare with other drugs.

7 Q. One other thing on the two
8 transparencies, Doctor, and the other one doesn't
9 really turn upon what is on the screen. You said
10 very little of the drug is metabolized, could you
11 please define for us metabolized.

12 A. Yes. Metabolized refers to
13 conversion of the drug to the molecular species
14 that are different from the parent compound. These
15 new entities are formed by enzymatic processes
16 that exist in infants and in adults and generally
17 occur as a consequence of enzyme activity occurring
18 in the liver, though not exclusively but primarily.
19 These compounds may or may not be biologically
20 active. As a rule, the body's defense is to
21 convert active drugs to inactive products, and
22 this is a detoxification process, but the wisdom
23 of the body is not absolute and sometimes it converts
24 these compounds into more active drugs, or into
25 drugs that are, may have equivalent pharmacologic



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activity. In the case of digoxin, though, while various products can be produced, the human, and this differs from animal studies, and humans in particular metabolize very little of it.



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In fact, one can find excreta in the urine, primarily intact digoxin. I used the figures 90 percent and 95 percent and I think those are figures that you will probably hear from others as well.

Q. Doctor, to this point we have got the digoxin either from oral or intravenous administration into the circulatory system and that is the delivery vehicle, is it not?

A. Correct.

Q. Where does it deliver the digoxin to?

A. I think I will go upstairs for a moment.

The point that we are touching on now is what happens to the drug once it gets into the circulatory system and as has been described, the drug in the circulatory system is not capable of exerting any pharmacological response. It only evokes a response when it contacts discrete areas in specific organs. These specific areas are called receptives. These are the target sites at which drugs work and appear to exert their biological effects.

The drug distribution pattern of any



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drug really depends on two primary factors. One is the affinity of the tissue for the drug, the so-called, I would say, the avidity with which an organ takes up a given molecular species and clings to it, so-called binding.

So you have this factor of avidity, affinity, there are technical terms, but I think this will define exactly what we are talking about.

If one has a series of organs with comparable avidity, the single critical determinant that influences how much drug goes to that organ is the relative amount of blood that is pumped out from the heart, how much of that blood really is distributed to that organ per unit time. So if you have something that will bind equally the determinant that regulates how much drug gets to the organ is the rate at which it gets to that organ. That is going to be a function of blood flow. So you have blood flow as another critical factor, organ blood flow; those two factors.

As I mentioned earlier, and I thought I would do it this way because there are going to be distinct, in the relative concentrations that might be achieved, depending on the route of administration of the drug - I do not want to confuse



1
2 you, there should be no confusion in your mind
3 that once a drug gets into the circulation, that
4 is the general circulation, not the specialized
5 circulation, the portal system, but I am talking
6 now once a drug gets into the general circulation
7 it is distributed in a fairly constant manner,
8 regardless of route of administration, once it gets
9 into that general circulation.

10 If a drug is administered orally,
11 as we saw on that diagram, you understand that the
12 first organ that comes in contact with the oral
13 drug is the liver. Therefore, it is very conceivable
14 that the liver will have a higher concentration than
15 another organ which may be the specific target that
16 we want to attack. For example, let us use digoxin.

17 When the drug is given by this route
18 it is very likely, and we know this to be true, that
19 if we were to measure the tissue concentration
20 shortly after giving the dose, in an hour, let us
21 say, we might find higher concentrations in the
22 liver than in the heart because even though we want
23 to affect the heart we are not interested in treating
24 the liver. We are interested in treating the heart.

25 Now, the distribution of the drug
therefore will to some degree, the concentrations
that are achieved in different organs, will to some



E 4

1
2 degree be influenced by this factor. As a rule, in
3 patients who receive a single intravenous dose of
4 digoxin, one finds very high, perhaps the highest
5 concentration in the kidney, followed by the heart
6 and the liver. As I told you, the kidney, this is
7 an intravenous injection, this is an injection where
8 the drug does not have to go through the liver
9 initially. Under those conditions the drug is
10 circulating in the blood immediately. Most of it,
11 no, a large portion - a large portion will be taken
12 out by the heart and an equally large portion will
13 be taken out by the kidney because both these organs
14 give very high blood flows and, furthermore, the
15 kidney is a primary organ through which digoxin is
16 eliminated in the body so that a lot of the drug that
17 you find in the kidney is not necessarily there to
18 exert a pharmacological effect but it is there in the
19 process of being cleared or removed from the body.
20 Very high concentrations can be found there. That is
21 with an intravenous injection.

22 With an oral injection, you may find
23 somewhat different distribution patterns. I am thinking
24 of the major organs. For those of you who want a very
25 elaborate organ distribution pattern, I will give you
a reference and you can go to that.



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2 The situation that occurs with the
3 oral route may be somewhat different in that you may
4 have a high concentration in the liver, followed by
5 the heart and the kidney. This is with single
6 injection. One thing we must remember is that when
7 we treat a patient we treat a patient over a long
8 period of time, and over a long period of time one
9 achieves what is called a steady state situation
10 so that the concentration, the total amount of this
11 drug presumably remains relatively constant over a
12 prolonged period of treatment. Obviously this is
13 very important because having this knowledge allows
14 the physician to determine when to change the dosage,
15 how much to change it by, and this gets into the whole
16 realm of kinetics; and I am not sure what Mr. Lamek
17 wants to do at this juncture.

18 Q. Just let me be sure that I under-
19 stand something that you have said, Doctor. You said
20 that following an intravenous administration of a
21 single dose, the highest concentration will be in
22 kidney and heart and I think you may have named
23 another organ.

24 A. Liver.

25 Q. The liver. Let me be clear. You
are referring to the time after the drug has been



1
2 delivered by what I call the transport system, the
3 circulatory system?

4 A. Yes.

5 Q. I am right, am I not, that
6 initially, immediately following that intravenous
7 administration, the highest level will be on the
8 transport system itself in the blood?

9 A. Yes. That is perfectly correct,
10 until it is distributed to the other areas in the body.
11 The distribution of that, the drug will circulate
12 probably between 2 to 5 seconds, I guess, and reach
13 other organs. That does not mean that the drug will
14 be completely taken up by the organs after reaching
15 them because these organs do not bind all of the drug.
16 Much of it continues to recirculate in the transport
17 system or circulation that we have just discussed.

18 Q. But eventually, as I understand
19 it, the train is going to be fully unloaded. The
20 digoxin will have been removed from the blood and will
21 have bound itself at particular sites in the body.
22 Is that correct?

23 A. That is true. Some will be
24 eliminated; some will be bound to tissue in the body.

25 Q. Are you able to tell me what
period of time may elapse from the time of



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administration of a dose, I suppose the size of the dose may be of some significance, to the point where there has been that full distribution of the drug to the tissues and organs?

A. I think maybe I can illustrate that point a little bit with another diagram.

Let me show you, looking at this one again, let us concentrate on the intravenous, you can see - I have them both here - you can see that following the injection, now, this injection, let us say, has been given to a patient over, let us say, a five minute interval - or it could be 15 minutes, a very quick injection.

You probably are a bit surprised at the very rapid fall in this concentration. It goes from about 7 roughly down to 2, almost within an hour or an hour and 15 minutes. That is a very, very rapid fall.

What is happening to the drug? To use the analogy that has just been projected, the transport system, the circulatory system, has all of the drug to begin with. As it is diffusing to the different organs, some of the drug is being taken up by these tissues. This very rapid fall is called the redistribution phase. Redistribution



E 8

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2 refers to the uptake of drug by organs in the body
3 and it is very crucial, as you recognize, because
4 it influences the amount of drug that is going to
5 be acting at a particular site.

6 This occurs, if an intravenous
7 injection, here, within an hour.

8 However, it is also clear, I hope,
9 that the drug does not disappear completely from the
10 body because if you follow it out with time you will
11 see we are still able to detect drug after 8 hours.
12 You see, the plateau is here. It is very important.

13 This low level, so to speak, is still
14 well within the prescribed therapeutic range for
15 effective therapy in a patient. So you have two
16 phases that I want you to concentrate on. One is the
17 initial distribution phase. This would have a
18 bearing as we talk about toxicity later on in the day,
19 the distribution of the drug and its persistence here
20 at what are therapeutic levels after the initial
21 distribution pattern.

22 Where does the drug go when it
23 redistributes? It goes two places. It goes to the
24 tissues and it is also cleared from the body. That
25 is, in the urine and perhaps some in the feces, but
primarily the urine. I think with some minor details



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that that would give you a better sense of it.

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2 The general information that is
3 available on digoxin will show, and let's -- it's
4 the middle column I want you to concentrate on,
5 please -- will show this. I summarized all this
6 and I can Xerox it for you if you like, you
7 see that the onset of action, that's the second
8 line here, is 15 to 30 minutes. It is really
9 extremely rapid. So that one can anticipate a
10 pharmacologic effect being induced not 15 or
11 30 minutes after oral administration necessarily,
12 but certainly 15 or 30 minutes after intravenous
13 administration. In fact, I would go so far as to
14 say that one could see an effect with this drug
15 within five to 10 minutes after intravenous administra-
16 tion. That would be either a therapeutic effect and/or
17 a toxic effect.

18 I don't know if it's -- some of the
19 other data we'll get to later and we can use this
20 slide to illustrate that point.

21 Q. Doctor, just before we leave
22 that distribution point, does it follow from what
23 you have said that different organs, different
24 tissues take up digoxin from the circulatory system
25 in varying amounts, or is there equal distribution
to organs?



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A. No, I think that it does follow that different organs will take up different amounts of digoxin. This is a function of their blood flow and the avidity with which the specific organ binds the drug once it passes through that organ in the blood system.

Q. All right.

A. There are data that can bear on this. I have citations that I probably should make available for the record.

An overall summary of this, I might say, is difficult to generalize on to begin with. However, we can achieve some consensus on this point if we bear in mind the conditions under which I am making these statements.

I have alluded to the fact that the compound digoxin when given as a single dose has a distribution pattern that, when given as an intravenous administered dose shows the highest concentration can be found in the kidney followed by the heart and the liver.

When it is given orally, there is a likelihood that one can achieve a higher concentration in the liver that may exceed the kidney and that



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then is followed by the heart; or the kidney and heart may be equivalent in this condition.

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Under so-called study state, when we are looking at tissue concentrations in a patient who has received the drug for a protracted period of time, and let me define that for you because I think that may be important, there is a specific period of time that is generally required for an individual to come to so-called equilibrium or steady state and that is about a week.

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So, about a week after administering the digoxin orally, one can assume there are steady state concentrations and this may be a little longer in some patients, two weeks, but generally a week to two weeks is what would be accepted.

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Q. Doctor, may I interrupt you just for a moment.

A. Please.

Q. You say about a week after administration. Do you mean after a week of regular administration and continuing administration?

A. Ah. I beg your pardon, that's very good. A week of continuous administration at



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regular intervals. Thank you very much.

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Q. Fine.

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A. Under those conditions we find

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that the general consensus in the published data

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would show that the highest concentration is in the

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ventricular -- and that would be the ventricular

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tissue of the heart, followed by the kidney, fol-

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lowed by the liver and by skeletal muscle.

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We can break this down into greater

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detail for those of you who are interested, but I

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think that this gives you something to work with

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and it perhaps will allow us to appreciate the

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difficulty we are going to encounter in dealing

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with interpretation of the tissue concentrations

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of these compounds.

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Q. One thing that is pretty clear

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from the list, Doctor, is that one cannot talk

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liberally of digoxin being taken out by the heart.

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One has to be rather more precise as to the particular

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site from the heart that one has in mind; is that

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correct?

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A. Yes, the truth is vague.

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Q. Indeed, the atrial muscle

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didn't occur at all in your list of leading positions,

did it?



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A. Ah! It didn't but I think

it is unfair to assume that it is not taken up
by the atrium. In fact, it clearly is and there
are studies that show that atrial tissue does take
up digoxin, though to an extent that appears to be
less than that of the ventricular muscle.

Q. Okay, Doctor, you have told
us that normally digoxin is eliminated through the
kidneys and urine. Do I take it from that that at
some point in its life that the digoxin that has been
bound to or deposited on the various tissues that
you have described and identified that is in some
way freed of them and eliminated?

A. Yes, I think that one must
recognize that in the curve that we have just looked
at where there is a very rapid falloff in the plasma
or serum level of digoxin.

As the serum or plasma level -- we have
plasma levels in the body -- begins to decrease with
time, if one were to stop giving the drug to the
patient, the drugs that were bound, that was bound
to tissue would begin to dissociate. That would
mean, would begin to leave the tissues and enter
into the circulation and then could be detected in the



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circulation if we were able to have an assay that was sufficiently sensitive to detect these low concentrations.

But the point is this, that we must distinguish between plasma concentrations of digoxin and total body accumulation. At the very best, the plasma concentration is an approximation of what may be in tissues.

Unfortunately, it is the best approximation we have at the current state of the art, but it by no means tells us what is actually in a given tissue. I think this can be illustrated in the following. Do we have just a minute?

Q. Sure, of course.

A. Now, there are two points that I want to see if I can get across to you. One of these relates to the accumulation of the drug. Now, when you are treating a patient we seldom, as I indicated, give the drug intravenously. We don't have to, most circumstances are not that acute. We can handle this orally, except in those special conditions where the patient cannot receive or accept the drug orally.

When we do that, we give a dose of the drug that is calculated to build up to a steady state,



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a constant concentration, and one that will not
adversely affect the patient.

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Now, if you start here from zero
on the ordinate you will see her it says, "Body
glycoside stores." This is a diagrammatic expression
of what I want to get across. It illustrates that
we are starting treatment in the patient and we are
at zero. When we get up to 100%, that's the
therapeutic goal that you and I want to achieve.

Now, in this circumstance here, we
are giving the drug at a fixed time every day and
you can see that in time, that is, five half-lives.
Now, a half-life is the time it takes for the
concentration of drug in plasma or tissue to reach
50% of its original level, that's all it is. So,
if the drug goes from 100 concentration, that's
from 100 to 50, and that's five-0 in one and a half
days, the half-life of that drug is one and-a-half
days.

So it is with digoxin, the half-life
of digoxin is one and-a-half days.

It is generally assumed, and I think
this is accepted by everyone, that five half-lives
of continuous administration, constant administration
of the drug, will achieve a steady state. So, you



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multiply five times one and-a-half days and that's virtually, roughly seven and-a-half days of regular dosage, appropriate dosage, you would achieve a steady state in a given patient who has average renal function, kidney function, etc., okay, it is a normal individual.

So, I hope this illustrates the rate of accumulation. You can see you approximate 100% at five half-lives and for digoxin, this is a day and-a-half for a half-life, and that's equivalent to seven and-a-half days.

Now, let's look at the question that was raised by Mr. Lamek. What happens when the blood level falls down. Suppose we stop giving the drug or the patient stops taking it. Let us say we are up here at 100% and we now go down, we stop taking the drug, you can see it clear into view. Could you follow me? That is to say, the elimination of the drug follows the same pattern of accumulation. It's a reciprocal curve, simple. That means when I stop taking the medication, not only does my blood level fall down, but that material that is in tissues also becomes released and goes back into the bloodstream and is eliminated through the kidney or some other process. I will



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leave that up there in case you want that document.

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Q. I must confess, Doctor, I am having a little difficulty with that. I think I understand the point you are making. May I ask why in the situation that you advance when the patient stops taking the drug or the drug is withdrawn and there is then a process of elimination of the drug which is being accumulated in the body or which extends over the same period of time that it took to achieve that steady state, I understand that, but in that process you say the drug is released from the tissues from which it has been bound back into the bloodstream and is then still eliminated. Why isn't it merely taken up again in the circulatory system by the tissues?

A. You ask the most devilish questions!

Q. Well, that's the advantage of being simple minded and unschooled in these things.

A. Well, okay. I think that the basis for this phenomenon is that the important point to remember is, the drug is not irreversibly bound to the tissue. It is a reversible phenomena so that when the drug is taken up by a tissue this means that not only can it be taken up, it can be



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released from that tissue.

The gradient, concentration gradient
from tissue to plasma is so extreme in this
circumstance that all of the drug that goes into
the plasma under these conditions then is able to
be cleared by the kidney.



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It is simply that the capacity and avidity of the kidney for clearance of the drug is such that all of the drug that is delivered to the kidney is a relatively small amount perhaps, can be cleared by the kidney during its passage through the kidneys. So that is why none re-enters into the circulation, presumably that is why.

Q. Now in referring to the transparency that is now put up on the screen, Doctor, I think you referred to normal renal function. Now if there were to be not normal renal function, what if renal function is impaired in the patient about whom you are talking, what then is the effect on elimination?

A. Very simply elimination is delayed and the half life of the patient may be prolonged from one and a half days to four or five days. So that if one were to continue with normal administration of the drug you would have accumulation exceeding the hundred percent that we show. When that happens, when you cannot eliminate the drug you keep filling up the pool so to speak. It is like dumping something into a bucket and having the drain plugged. If you continue adding the drug it accumulates, and since the body cannot metabolize



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this drug very effectively, you get extraordinarily high concentrations developing in the patient and this leads to toxicity, or may lead to toxicity.

Q. Doctor, I have noticed so far that in some of the questions that I have asked of you I have been referring to blood, and some of the answers you have given me you have referred to serum, and in others to plasma. Are we talking about the same thing, or different things, and if the latter, what is the difference please?

A. The general measurement of concentrations in biological specimens taken from the human are carried out in either serum, plasma or in some cases whole blood.

Traditionally, digoxin serum has been used, now serum is the liquid that is left when blood is allowed to clot. In some cases plasma has been used. Plasma is a liquid that can be obtained from blood when the fixed or cloned elements, that is the white and red cells, are removed.

Now generally the way plasma differs from serum is that plasma is blood that is not allowed to clot and one uses something, an anticoagulant such as heparin to prevent clotting of the blood.

Then finally there are measurements



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that are made with whole blood which would include both the plasma, and the red and white cells. Those measurements are generally quite unusual in terms of digoxin units and generally the former are used.

Q. Now, Doctor, obviously we are interested here in digoxin in a pediatric setting and those are the two areas of your specialization. Can we talk for a moment about pediatric administration of digoxin? Is there in clinical practice a generally accepted guide, or rule of thumb, for the calculation of the dose to be delivered to a child to produce the desired therapeutic effects?

A. Yes. This has been established quite accurately I think for children of different ages, and the guidelines are very clear. I think they are well accepted blood or concentrations of dosages I guess is a better term of the digoxin that are used in the States and in Canada.

Q. You say children of different ages, is age a significant factor in the equation?

A. Yes, it is. I have here tabulated for anyone who wants this, a tabulation of the recommended digitalized doses of digitalis that I can give you and I will get back to that in a moment.



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To answer this last question, yes, age, is age an important factor I think was your question?

Q. Yes.

A. Yes, it is. It is becoming quite apparent that children of different age groups have varying degrees of sensitivity to digitalis. The available data would suggest that the dosage unit dosage of digitalis, or let us use digoxin so I don't confuse things, the digoxin that is used in infants versus that which is used in the adults is such that the infant receives the equivalent of twice the dose an adult gets per unit of weight, twice.

Q. Can you define infant for us please?

A. Oh, a neonate, is an infant of 30 days of age. An infant is a child up to one year of age, et cetera. I think all parents know what happens after one year, toddlers.

Q. They may describe them in different terms.

A. Well some people might describe an infant up to 24 months. What I am trying to define actually are different metabolic states and different states of pharmacologic reactivity that are associated



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not only with ontogenesis, but are associated with human development.

The study of developmental pharmacology really is an attempt to codify and define these extraordinary differences that maturation, biological maturation impart on the capacity of the individual to respond to xenobiotic substances, and in this case drugs. It is profound. For example, while I give you this generalization, it is - I said that the dosage of drug that is given to infants is twice that that is used in the adults on a weight basis. The exception to this statement would be premature infants who are extremely sensitive to digoxin and will get lower concentrations, and probably children within the first week or two of life, or neonates. They appear to be unusually sensitive to drugs and it is - there is also some suggestion that low birth weight infants are a bit more sensitive.

Now, that is probably a reflection of the varying degrees of biological maturation in these individuals, or in these children. I think I got off the track somewhere, where am I?

Q. I was asking you about whether age was a critical factor in the equation to determine therapeutic doses.

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A. Well, I think I answered that.

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Q. Yes, you did indeed, you didn't
get off the track at all, Doctor.

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How as a clinician do I know whether
the dose which I have selected and administered is
producing a therapeutic and not a toxic effect in a
child?

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A. Sometimes it becomes a very
harrowing and extremely difficult situation. The
diagnosis of congestive heart failure is considered,
I think by most clinicians, to be a clinical diagnosis,
and I think most experts would concur in that view.

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Likewise the response of the individual
with congestive heart failure to digitalis, or
digoxin therapy, also must be viewed from an empirical
perspective and there are some clinical guidelines
that we use. A child with congestive failure, or
heart failure, will feed poorly, may have fluid in
the lungs, have difficulty breathing and having a
rapid respiratory rate, may be gaining weight, that
is may be gaining fluid, and fluid is not eliminating
adequately, may have enlarged liver and spleen,
protuberant abdomen and generally is an ill child.

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The treatment essentially, the decision
or determination of adequacy of therapeutic response



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is elimination of these signs and symptoms among which I have listed I think five major ones, and that is how the clinician makes a decision.

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It was hoped that this could be quantitated more effectively and I am sure we will discuss how the blood level or plasma level assist the clinician in making this decision of adequacy, but I think it is important to recognize at the onset that this is a very very clinical and empirical process.

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Q. Doctor, that is going to take me next into a series of questions about the symptoms of toxicity and the interpretation of serum levels and I wonder, Mr. Commissioner, if this is perhaps an appropriate time to break for lunch?

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THE COMMISSIONER: Have you any idea as to timing?

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MR. LAMEK: I think if we were to take only a slightly shorter lunch break than we normally do today, sir, we will finish comfortably this afternoon.

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THE COMMISSIONER: All right, 2:15.

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MR. LAMEK: 2:15, thank you, sir.

--- Luncheon adjournment

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---On resuming

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MR. LAMEK: Mr. Commissioner, the witness will be here directly, but perhaps before he returns could I say two things.

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First, the various transparencies to which Dr. Mirkin has referred today will be copied and made available to all counsel. Perhaps it might be appropriate when we have a bundle of them together, to mark them as an exhibit. Perhaps we could reserve the next exhibit number for it -- Exhibit 6.

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THE COMMISSIONER: How will we describe them?

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MR. LAMEK: Q. How will we describe them, Dr. Mirkin, the transparencies that you explained this morning? Can we have a collective or a generic term for those so we can describe them as an exhibit?

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A. Audio-visual celluloids.

Q. Audio-visual celluloids. I

like that. It sounds like a pharmaceutical preparation.

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A. Or hemorrhoids.
MR. LAMEK: The second, Mr. Commissioner, Dr. Mirkin has agreed, if any counsel would like to take advantage of this, to make himself available to counsel at the end of today's hearing, I suggest in one of the hearing rooms up at 180 Dundas Street, as



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I think we should try and clear this court room
as soon as we conveniently can after the end of
the hearing, for not an inordinate length of time but
to assist counsel in understanding the evidence
today or clarify any questions in the hope that
it may help them prepare for cross-examination
at a later stage.

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THE COMMISSIONER: That is certainly
very helpful. You realize, counsel, that I will
not be there and the reporters will not be there
so whatever treasures you may glean from Dr. Mirkin,
if you want to put them on the record you will have
to do so the next time he is available for cross-
examination.

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That is something, though, that would
help considerably, because it may clear up a lot
of lines of investigation which I would want to
undertake which would not be productive, so that
I recommend any of you who have any questions of
that nature to take advantage of it.

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MR. STRATHY: Dr. Mirkin indicated
that he had details of references or citations that could
be distributed that would assist us. At some point
could these be distributed?

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MR. LAMEK: I think I can do better
than that for Mr. Strathy. He is quite right. I



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propose to have those papers, articles, whatever
they may be, copied and distributed as well.

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THE WITNESS: If I could interject
a comment, my only concern and I do not know if
it is a legitimate one, but I presume I should
mention it, is the patent requirement. Some of
these are copyrighted articles. In the States
there has been some concern about that, whether --
as far as I am concerned, these are open literature
for you to use, whether I am properly allowed to
Xerox my copy, to duplicate them and send them to
you, I do not know. I think I have to rely on
counsel's advice. He has already advised me.

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THE COMMISSIONER: What did he say?

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MR. LAMEK: I think there are two
possible answers. Number one is to have the
Commissioner perhaps require you to do it and then
you would be responding, of course, merely to
the wishes of an officer with terrible contempt
powers or to provide me with the references and I
will take my chances on having them copied and
distributed. We can work our way around it. We
can resolve it.

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THE COMMISSIONER: All right.

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Q. Just one thing that I would like



1
2 to clear up, Dr. Mirkin, from before lunch, if
3 I may. When you were talking about the dosages that may
4 be appropriate for the small children at least
5 to achieve a therapeutic result, I understood you
6 to say that it is well established that an infant
7 dose may be twice per unit of body weight the adult
8 dose. Do I have that correctly?

9 A. That is correct.

10 Q. Could you just explain what
11 that means? You don't mean in absolute terms the
12 child takes twice the amount of digoxin as an
13 adult will take?

14 A. No, but what we are talking
15 about now is the amount of drug that is given per
16 dose as expressed per unit weight or body surface
17 area, which is another reference point, reference
18 measurement, I guess, that is used in children
19 in developing a dosage.

20 For example, if a newborn infant
21 would receive a dosage of 30 micrograms per kilo-
22 gram, an adult equivalent might be 15 micrograms
23 per kilogram.

24 Q. Therefore, a child weighing
25 approximately five pounds, two kilograms, on that
basis would receive 60 micrograms?



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A. Correct. The total dose

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would be probably less in the infant as compared

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to the amount given to an adult, but the amount

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per body weight would be more in the infant rather

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than in the adult, correct?

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Q. Yes. It is a function of

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body weight you are expressing there?

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A. Correct.

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Q. We had reached the point, just

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before lunch, Doctor, of toxicity. Perhaps you could

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tell me, please, what are the known symptoms of
digoxin toxicity?

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A. The major effects are on the

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rate and rhythm of myocardial contractility.

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That is to say, the digoxin effects, this is now
the toxic effects we are talking about --

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Q. Yes.

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A. --the major toxicity effects

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are the effect of the drug and rate and rhythm

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of the heart. Early this morning I was attempting

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to describe the effects of the drug on the

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conduction system of the heart. The conduction

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system is the system of the heart that does two

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things: one, it initiates heartbeat; secondly,

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it allows propogation of the heartbeat once

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it is initiated in the atrium to reach the ventricle.

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These are two important functions of the specialized

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tissue of the heart. One is, I will repeat those,

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to initiate the heartbeat and secondly to allow

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propagation of the initiated heartbeat from the

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atrium through into the ventricle.

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Digitalis has a profound effect on

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those. When one has an overdose of digitalis in

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the body one sees so-called rhythm disturbances.

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A major side effect is decrease in the conduction

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between the atrium and ventricle so that the

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ventricular rate is disassociated from the atrial

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rate and to an extreme one has complete disassocia-

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tion of these beats and what is called AV block,

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atrial-ventricular blockade occurs. That is a side

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effect of extreme toxicity.

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As a consequence of this, as one

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increases the concentration of digitalis in the

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body, one also has increased automaticity.

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By automaticity we mean the capacity of the

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tissue to spontaneously initiate a beat.

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As you can imagine, if you have a

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drug causing different parts of the heart to

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initiate its own beat, you have a heart that is

beating in an asynchronous manner and this discordancy



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in beating produces an ineffective heartbeat so
that the normal pumping of the heart will be
diminished.

If allowed to go to an uncontrolled
situation you have what are called premature
ventricular extra systole. I am sorry to beseige
you with all these silly names --

Q. Could you spell that for us,
Doctor?

A. Ventricular extra, e-x-t-r-a,
systole, s-y-s-t-o-l-e. I will define that for you.



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Systole is a complicated way of talking about the state of contraction of the heart. When the heart is contracted we call it systole, when the heart is relaxed we call it diastole. Okay. When the heart is contracted we call it systole, when it is relaxed we call it diastole, d-i-a-s-t-o-l-e.

So, we have systolic and diastolic.

The digitalis increases the force of contraction and the force of systole is as a consequence of giving it. When too much is given, you not only inhibit the conduction, but you increase the automaticity of the heart so that it starts beating in a way, in an uncontrolled manner, extra beats start coming into the cycle. These extra beats are called extrasystolics. I use the term premature because they come out of the normal sequence, they come before the normal sequence of events. So that premature ventricular extrasystoles, there is an extra beat. Someone, if you have gone to bed at night and you had, sometimes you will get a thump, you have the feeling that your heart sort of stops, that's it. You know, that happens all the time.

Now, it is caused by a drug. It can be a very life threatening problem. This is a very difficult business. So, if carried to an extreme, the



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2 heart develops what's called ventricular fibrillation
3 where the heart is beating or the ventricle is beating
4 in a manner that is non-productive. It's been
5 described as a bag of worms. If you can visualize
6 any one of fishes or a bag of worms wiggling, a very
7 non-productive contraction of the ventricular muscle.
8 That's ventricular fibrillation.

9 That will lead to no blood being pumped
10 out and that will lead to a very rapid demise of the
11 patient.

12 So, to recapitulate then, the major side
13 effects or toxic effects are those on rhythm, on the
14 conducting system, number one; number two, production
15 of extraventricular, extrasystoles, that is, abnormal
16 beats and production of ventricular fibrillation
17 eventually.

18 Very often, if one gives a very large
19 amount of digitalis, one can produce complete
20 contractions, almost where the heart goes into spasm,
21 it contracts on itself. That's something that is very
22 rare, of course, and it's the kind of spasm that the
23 heart can be thrown into by very large concentrations
24 of digoxin.

25 So, I think those are the primary
adverse effects that you should be acquainted with.



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Q. Is slowing of the heart beat a symptom of digoxin toxicity?

A. Well, the major thing, the major event as far as rhythm is concerned is a change in the efficiency with which the heart rate is propagated from the atrium to the ventricle. So that one can have a situation where the atrium is beating at a normal rate and the ventricle is going at its own rate. So that this is called idio, i-d-i-o, idio-ventricular rate. In that condition, the ventricle assumes its own rate, which is generally slower than a normal heart rate. That may be 40 to 50 beats per minute, whereas, the atrium is probably beating at 80 to 100 beats per minute. So, you have dissociation.

In that sense, you may perceive it to be a slowing of the heart rate.

Q. Okay. Now, are the changes in rhythm that you described, Doctor, detectable by EKG?

A. Oh, yes, very clearly.

Q. Are there any other symptoms that are associated with digoxin toxicity? Perhaps not so specific as those, but other symptoms?

A. Well, there are a lot of symptoms that I guess would be well in the realm of non-cardiac



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symptoms. For example, nausea and vomiting are very commonly associated with digitalis intoxication. The nausea presumably may come from irritation of gastro-mycosis, although, that is dubious in my mind. More likely the nausea and emphasis arises from stimulation in the central nervous system of so-called emetic vomiting centres which are well defined in the central nervous system.

These drugs, cardiac glycosides, digoxin, are well known to produce central nervous system effects as well. So, emesis, nausea.

You also have other central nervous system effects: visual hallucinations, particularly a very well described one is having nightmares in technicolour, having dreams in very vivid colours, I've always been intrigued with that one.

Whether or not confusional states can arise from digitalis per se I think is a moot point, but it is described. Certainly there are probably several pages of other side effects, but I think these are the major ones: the heart, central nervous system, the gastrointestinal tract.

Q. Now, Doctor, recognizing that serum levels in living patients who are following a regime of digoxin administration may not be any clear



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indication of toxicity, nevertheless I understand that serum levels in such patients are frequently monitored. Is that so?

A. That's correct.

Q. And to the extent that those serum levels are capable of, if not indicating toxicity, at least alerting the physician to the possibility of toxicity, can we now address the levels in serum, please?

First, may I ask you this though? Are there any conditions in a patient which may make him more sensitive to digoxin than perhaps a patient without this condition may be? Are there any, if you like, predisposing conditions of toxicity?

A. Yes, there probably are several states that may occur which render the heart more sensitive, more sensitive to a given concentration of digoxin. I think I've mentioned one or two of these previously.

These would consist of the following: one would be a significant decrease in the serum potassium concentration, assuming that this was also paralleled by a fall in the tissue, potassium concentration as well.

Another fact that might make the



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individual more sensitive would be an increase in the
calcium concentration, both in the serum and presumably
in the cell.

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There are endocrinopathies, that is abnormalities of the endocrine system, which are also presumably sensitized, the heart, and one of these would be hypothyroidism, I guess.

Q. Hypothyroidism?

A. Yes, I think it would be that.

I was confused, hypo or hyper and I will check my notes to make sure about that.

I think individuals who also have intrinsic rhythm defects should be carefully evaluated before given digoxin. For example, individuals who may have very, who show a tendency let us say to spontaneous extrasystoles as I just talked about before, there are people who have this problem yet are not taking any drugs, and those people if you give digitalis or digoxin to those individuals you are liable to make that situation considerably worse. So that should be of some concern because the situation that occurs in diseased hearts is such that very often one sees abnormal rhythms in a diseased heart without any drugs being present and that makes our situation very difficult to evaluate, and we may get into that later on. Imagine the scenario where an individual, or a specific heart is showing an abnormal rhythm, ventricular rhythm and then to that situation you



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add digitalis based on what I have told you that
will make that situation worse.

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Other situations that appear to
influence the response of the heart are changes in
the acid base balance, that is to say PH and the
acidity of the blood. I would say as a general
statement that individuals who are more acidic are
probably more sensitive to digoxin.

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Then of course there are other
circumstances and I will not get into alitany on this,
patients who have poor renal function but that is
the secondary cause I think.

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Q Doctor, we have heard last week
that the radioimmunoassay for digoxin is something
less than about 15 years old and indeed as I read
your CV I think I am correct in saying that you are
an author on one of the early papers on RIA and
serum of digoxin in children, were you not?

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A. Yes, that is right.

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Q In your view is RIA, radio-
immunoassay a satisfactory analytical technique for
establishing the presence and concentrations of
digoxin in serum?

A. I think under most circumstances
it has proved rather satisfactory, that is in



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individuals of given age groups.

Q. Could you elaborate on that a little bit?

A. Well, I am able to make that statement, I wouldn't have been able to make it a year or two ago. First off the immunoassay, and I think I can illustrate this a bit more if I show a transparency.

I have been told that you have had considerable exposure to this but it occurred to me that perhaps you didn't see it in this visual manner. I dug this up from something I haven't looked at since 1973, it is still valid.

Let me, if I may, if this will help some of you, I don't know, give you an idea of just what these words mean.

First off, you have heard of immunoassay. Essentially what we are talking about is the production of an antibody. Now an antibody is something that is produced in a biological system, it is sort of a natural defence of the organism to foreign proteins, to foreign substances. When anyone in this room ingests a foreign substance, the body has the capacity to develop an antibody to it, provided that substance will give sufficient antigenic



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stimulation. That is to say, provided the body sees that material as a foreign substance. Once the body sees it as a foreign substance, you, I, anyone in the room will make antibodies. People with cancer do not make antibodies in the normal way. People taking anti-cancer drugs, people taking drugs that are used for transplant rejection reactions do not make antibodies in an effective manner.

However, the whole process of immuno-assay is contingent on the capacity to develop an antibody. The antibodies that we used, or that were used in the assay, are not developed in patients, they are developed in animals, so an animal is given digoxin in a modified manner and an antibody is developed to it. These antibodies are purified and are available as kits. A kit can be purchased by the hospital, or by anyone who wants to measure this.

Now, when I am measuring the serum, or you are measuring the serum in digoxin in a serum or in a tissue, what we do essentially assume that there is digoxin in the tissue and if we put an antibody in the same medium that digoxin and antibody will form a complex, okay, that's it.

Now, the whole assay procedure is dependent upon being able to quantitate the



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concentration or amount of digoxin in a patient's serum. If I were to add digoxin to a patient's serum without being able to distinguish what was already in there, I could not detect it.

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Now, the way I can do this is to take digoxin, which is labelled with a radioactive substance, in this case tritium. That is radioactive digoxin and if I take the radioactive digoxin, put it with the antibody, I end up with digoxin radioactive antibody complex. The same complex as occurs with digoxin and the antibody on top.

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The whole idea of the assay is to take the patient's blood, the serum this time, that contains digoxin, okay. We add a known amount of the digoxin radioactive to it and a known amount of antibody and we form a complex. The binding of the antibody to the digoxin occurs in the same manner as the finding of the antibody to the radioactive digoxin. So if they are both there in the same tube the antibody will equal affinity and that enables us to say that if there was more of this, that if the patient has a very high concentration, less of this will be found. If there is less of this in the patient, more of the tritium will be found. Essentially the relationship between the non-radioactive



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and the radioactive which is what we are measuring, simple. I think this will show you how it is done. You have the radioactive digoxin and the digoxin antibody mixed up, we incubate it for 30 minutes here, we add a little charcoal, spin it around, centrifuge it and simply take off the supernate, that is this material here, and measure it, a very, very simple business.

Then you generate a standard curve, and I am going to quit right now. What I want to indicate to you, this is the way it is conventionally reported in the literature. What we are looking at is sort of competition between the non-radioactive digoxin and the radioactive digoxin and we make a standard curve and based on that relationship I can see what I have in the patient's serum. I realize it is a little technical but I wanted to attempt to illustrate it for you as best as I am capable of doing.

This enables us to make measurements not only in serum but in tissue. To get back to I think a very seminal issue and that is how specific, how useful are these things. Can anybody indeed discriminate? I am not sure if someone said the human body is capable of making, I don't know how



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many thousand, how many million different antibodies, a hundred thousand to a couple of million different antibodies, different substances, and these are very, very discriminatory.

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Unfortunately the antibody that we make for digitalis or digoxin has an overlap and it does cross-react with some of the metabolites that may be produced by digoxin.

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You heard me say earlier in the day that digoxin is poorly metabolized in the human body, but even though it is poorly metabolized some metabolites are produced and these can cross-react. If those metabolites for one reason or another accumulate in the patient's sera, then this could cause some confusion in interpretation of these data. I would submit that in patients with normal renal function, that is not a major source of contamination, or cross-reactivity. It may be other substances in newborn infants that we can get on to a bit later that will cross-react and give abnormally high concentrations of these materials, that is, will give a misleadingly high assay result and that is something we can discuss a bit more because it is very recent information that suggests the presence of this material in the sera of newborn infants.



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So I think what we have defined here are some rather specific concepts related to the immunoassay and I hope I have touched on very briefly some of its limitations.

Q Dr. Mirkin, you have referred to the lack of complete specificity of the antibody that is used in the digoxin immunoassay. Do I infer from what you said that is what you regard as the major disadvantage of that analytical technique?

A Yes, I think that would be my conclusion.

Q We heard last week that to the extent that the metabolites of digoxin are known and identifiable, that by a process of high-pressure liquid chromatography they can perhaps be screened or separated out of the sample that is going to be put through the immunoassay, you are familiar with that technique?

A Yes, sir.

Q And do you regard that as a satisfactory technique for isolating in the sample the digoxin as opposed to the digoxin metabolites?

A Yes, I think that is an adequate mode of isolation of the metabolites, provided the metabolites, once taken off the HPLC are further defined by mass spectrometry.



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Q. In other words, once you have confirmed what one is taking off and screening out is really the material that you want to exclude?

A. Yes, that would be the ideal case. One could make a reasonably secure judgment by using standards of these metabolites, running those on the liquid chromatogram and using the pattern that you see, comparing the pattern in an unknown specimen with the knowns. That is used to a large extent, these days.

Q. We may still have to grapple with the unknown or unidentified other substance, other than the known metabolites. Can we come to that later?

Could I ask you now whether there is a generally accepted range of serum digoxin levels in children, that is thought to be consistent with therapeutic dosage, or therapeutic effect more significantly, I suppose?

A. Yes, I think there is a large body of information, and I have a table here that I can - we can reference at appropriate points.

I have a transparency of those figures. Do you think I should flash that?

Q. Sure. That would be useful, I think.



DD 2

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THE COMMISSIONER: These transparencies, we have no machine like that. What is the merit of having the exhibits which we can't --

MR. LAMEK: I think we can reproduce them in a readily readable form, Mr. Commissioner.

THE COMMISSIONER: Can I just see one for the moment?

MS. CRONK: They can be photocopied and printed.

THE COMMISSIONER: Oh, all right. We are going to do these without the machine?

MR. LAMEK: That is right.

THE WITNESS: These are made from this document.

THE COMMISSIONER: All right, thank you.

THE WITNESS: This is a table that was taken from an article by Dr. Singh, S-i-n-g-h, published in a book that I edited called "Clinical Pharmacology: A Pediatric Perspective" published by Year Book. They are returning copies now. It is the only book where the editor had to pay royalties.

I think that what we have here is a series of blood levels in different aged children, new-borns on top; infants, 1 to 12 months; and children,



DD 3

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2 and what you can see is an interesting depiction, I
3 think, of the amount of drug that is used for the
4 daily maintenance dosage and the actual blood level,
5 serum level that is achieved in the patient. This is
6 a compilation of a large number of studies and I think
7 that the maintenance dose is a bit confusing. I will
8 give you another transparency to show you that in a
9 simplified form but what is quite clear here is that
10 in newborn infants, from 0 to 30 days, the range of
11 blood levels ran from 1.8, let us say, the average,
12 1.8 to 2.1. Actually it is 1.5, I guess, to a high
of 3.8 in this study.

13 So you can see all of the other studies
14 and there probably are some more that have been
15 published since 1978 that are readily available for
16 you.

17 I would say, though, that an average
18 serum level in this age group probably is in the order
19 of about 2 nanograms per mil. Let us sort of use that
as a working range.

20 As you get older, I think you can see
21 that on the bottom panel the children, these are
22 children now, talking about children more than one year
23 of age, the levels tend to be lower, in the order of
24 about 1 or 1.4, something like that.
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DD 4

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In children, those begin to approximate the so-called therapeutic dose that is seen in the adult. The point that I think has to be emphasized here is that we are not really sure what a therapeutic blood level rep means in this population and I think that gets to the hub of the matter.

I have a few slides that might illustrate that, or do you want to wait on that now? Shall I show those? What would fit in?

Q. Perhaps it would be more convenient if we could come back to the slides, Dr. Mirkin. There are a couple of other things that I want to cover. If you have some depiction of the thing that you think would be helpful, perhaps we could come back to that.

Linking that last piece of information to what you told us this morning, Doctor, as I understand it the digoxin that is in the circulatory system is not doing its thing. It is not being biologically active at that stage. It is only biologically active when bound to organ or tissue -- or is only capable of being biologically active when bound to organ or tissue.



DD 5

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A. Correct.

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Q. Therefore when you are measuring serum levels of digoxin essentially what you are measuring is digoxin that is having neither therapeutic nor toxic effect?

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A. That is correct. However, --

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Q. It reflects, I take it, and

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there is a correlation I take it between what you are discovering in terms of blood level and what you are inferring therefrom in tissue levels?

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A. That is correct. That is the basis for use of these modules.

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Q. There is no magic in the blood level in itself except as a basis for inferring a concentration in tissue, and I take it in particular in heart tissue, that will do the therapeutic job?

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A. That is correct, and I think that is a very clear point. It is explicitly stated and can be taken at face value.

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Q. Or taking it one step further, you are inferring a level in heart tissue that may be doing more than a therapeutic job, may be doing it at a level where it is producing toxic effects?

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A. Yes, that is correct.

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Q. That is the reason that you

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DD 6

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monitor the blood level in children who are receiving digoxin, is it not?

A. Yes.

Q. The kind of range of serum levels that reflect what I call therapeutic loading of the heart, can I put it that way, that kind of range I take it is by no means a fixed and definite range. How much elasticity is there in that?

A. I think a range by definition would imply some flexibility in the concentration of a drug that would be required to produce a given response, by the term range.

What has been accepted in the adult, if I may go back to that, that concentration that exceeds 2 or 2.5, it depends on what range study you use are characteristic of digitalis intoxication. This is in the adult.

However, when one looks at the strict interpretation of the data, and I have a slide to show that here, one sees that there is a considerable overlap where many individuals will have blood levels that exceed that concentration and they are not considered to be intoxicated, clinically, with this drug.

So that I think it is important to recognize that these are not absolute indices, that is



1
2 the serum concentration is not an absolute index or
3 predictor of intoxication.

4 Now it gets a little more complicated
5 or more ambiguous, I think, in the infant because here,
6 as I mentioned, the young infant as you can see can
7 tolerate a higher blood level to begin with. In fact,
8 normal therapeutic approach mandates that we use a
9 larger amount of drug per unit weight in the young
10 infants.

11 Consequently, we normally achieve higher
12 blood levels and I would say that most individuals
13 would not be too uncomfortable to accept blood levels
14 in young or infants that are between 2.5 - I will even
15 go as high as 5 nanograms per mil, but I think 5 is
16 stretching it a bit. I would say about 2.5 might be
17 the upper limit that we would be willing to accept,
18 looking at the patient, but it would not be unusual,
19 I might add, for children, infants, to have blood
20 levels of 4 and 5 without any demonstration of toxicity.

21 So for the purpose of our discussion
22 we are talking about a range of 2.5 to 5 and I think
23 that many, many patients are carried at that level.

24 THE COMMISSIONER: Mr. Lamek, can we
25 have that table as an exhibit?

MR. LAMEK: Yes, I am proposing,



1
2 Mr. Commissioner, to mark all of these transparencies
3 in printed, and therefore more legible, form as an
4 exhibit.

5 THE COMMISSIONER: We are saving the
6 other ones as number 6. Do you intend this to be part
7 of number 6?

8 MR. LAMEK: Yes. Perhaps we could
9 call them all number 6 when we have them all in, Mr.
10 Commissioner.

11 Q. Can we explore that just a little,
12 Doctor. If you were to record serum level in an
13 infant, I am speaking now about ante mortem blood
14 sample, the serum level in an infant of let us say
15 5 nanograms per millimetre, can you safely assume
16 that that represents the therapeutic level of
17 digoxin in that child?

18 A. Yes, I think you could safely
19 assume that. If I understand your question, you are
20 not asking whether you could safely assume that this
21 would be a toxic level but that certainly would be
22 expected to be giving some therapeutic response.

23 Q. Yes, would be giving some thera-
24 peutic response.

25 A. You would anticipate you would
see one.



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Q. I am trying to draw, if I can, and
it may be inappropriate but I am trying to draw, if
you like, a barrier at the point where toxic effects
may begin to be seen.

A. I am going to have to be rather
vague on that particular issue because I don't think
I can specifically answer it with the information
currently available and that is to say categorically
that any level above 5 will produce untoward effects
in the patient. By untoward effects I mean toxic
effects in that patient.

- - - -



EE
BB/PS

1 Q. I take it, Doctor, you could
2 not say categorically that a level below five might
3 not produce untoward effects in the patient.

4 A. That's correct, certainly.

5 Q. There is, in other words, a
6 considerable area of overlap or greyness there.

7 A. Yes, I think, in looking
8 over levels that we reported in our work, the
9 average, I think, was about 2.1, but these are
10 normal maintenance doses of digoxin.

11 But the issue is whether or not any
12 specific level above 2.5 can be described as
13 being 100% consistent with the production of
14 toxic events in that patient.

15 I think the answer to that question,
16 as I raise it, is no.

17 Q. Fairly, Doctor, if a level
18 above 2.5 nanograms per millilitre. is recorded
19 in the serum of an infant who is receiving
20 digoxin treatment, should an inquiry be made, in
21 your opinion, to ensure that no toxic results are
22 flowing from that level?

23 A. Well, I think here you also
24 have had varying viewpoints. In my judgment, it
25 would be incumbent upon the physician perhaps to
question carefully any further increment in the dosage



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of that individual. The reason I bring this up is that I, as the treating physician, would have to discern whether the patient was achieving the maximal effect possible with the drug or whether that patient indeed needed more to bring it up to, let us say, four, at which point I would see a better clinical response.

Here we get into the clinical empiricism of what I attempted to describe earlier. The therapeutic effect, the assessment of this, is purely a measurement of the clinical response because in many of these patients at concentrations of 2.5 nanograms per mil, one may see some electro-cardiographic changes that are consistent with so-called digitalis effects.

Now, I hope that point is clear. That at 2.5 you may see some of the changes that are consistent with digitalis effect, yet the patient may not be demonstrating a beneficial or sufficiently beneficial response to the drug treatment. When I talk about effects, I am talking now about the discernment of that effect by use of electrocardiogram. Electrocardiogram gives us certain information about the effect of digitalis in the heart, on the heart. It cannot be used to define whether or not that amount of drug is



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producing a sufficient clinical response. Only
clinical observation, I believe, can give that.

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Q. Well, let us go for a

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moment substantially beyond the order of numbers that
you've been talking about. If in a child who has
been receiving digoxin on a routine basis a level
of 8 or 9 nanograms per millilitre were recorded,
I take it that would be cause for investigation

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by the physician in charge of that case.

8

A. I think that's reasonable to

9

assume.

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Q. Is that because it is reasonable
to regard levels of that order as likely to be
consistent with toxicity, or reflective of toxicity?

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A. I believe if we are talking

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about a situation that would accrue following

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constant administration of the drug, that is at

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the steady state situation we talked about before?

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Q. Yes.

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A. Then I think most reasonable

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people would think there is reasonable reason for
alarm and concern at that blood level.

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Q. You seem to be drawing a

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distinction there, Doctor, between that kind of

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level appearing in a child who is on a regime of

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digoxin therapy and some other situation. What's the other situation that you have in mind?

A. Well, I think throughout this dialogue, and particularly this morning, I mentioned some changes in the behavior of the drug and perhaps the patient when exposed to a single acute dose of the drug, remember I talked about differences in distribution with the IV and the oral route following a single dose and then we talked about something, what happens when the drug is given chronically.

Now, we have had experience where ingestion of the drug, large amounts of non-therapeutic, these were essentially acute ingestions which are poisons where a patient has reported, oh, something like 55 nanograms per mill, this is an acute ingestion of a patient who did not receive the drug chronically, and I believe, I would have to check my records, had normal heart. This child experienced this high concentration with no arrhythmias, no sign of any effect and left the hospital in 24 hours.

Now, that's a single acute dose. Now, you should not walk away from our discussion with the conclusion therefore that high blood levels do

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not mean anything. I think, what I believe this demonstrates, is that a single acute does may not produce the hazard sequela that one sees with elevations, even of ten in a circumstance where the drug is being given on a continuous basis. So that not only do you have a serum concentration, but you have a tissue concentration which is sustained at that high level.

I hope that point is -- that I am sufficiently clear on that point with you.

Q. I think so, Doctor. But fairly as I understand what you are saying is that the single acute, even very substantial dose may not cause intoxication or the unfortunate symptoms or sequela of intoxication. Equally, I suppose it may well produce that sequela.

A. Exactly. I'm glad you brought that up. We can't use anecdotal experiences of that sort, though ours is recorded in the literature, in our paper. I think it would be misleading to use that kind of anecdotal information to exclude the possibility that an acute intoxication could indeed cause a toxic event in the patient.

Q. Doctor, you almost contrasted the situations of the patient who is receiving what



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you call chronic dose, the regular and maintenance dose of digoxin from the one in which the individual is administered a single acute dose. What if the two situations are brought together? What would be the situation in the case of a child receiving on an ongoing basis the maintenance dose of digoxin who then receives an acute and substantial dose. What would the pattern be there, in your experience?

A. Well, I don't really have ---

Q. I am sorry, your experience or review of the literature or both.

A. Yes. I don't have that sort of experience, but I think it is safe to say, and this again probably is going to be very difficult for us to confirm in adequate terms, and I regret to say that, but I will go on a bit. I think that an individual who has an already existing therapeutic level of the drug who is suddenly exposed to an inordinately large amount in an inordinately brief period of time, such as might occur after an intravenous administration, for example, would be prone to a significant risk here. That is, I think, as much as I can say now. I probably would have to go back and see if that kind of specific question can be answered in the literature. It may be, but



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with that in mind, I will try and go back and look
at that.

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Q. Thank you. Now, Doctor, I think you, as I recall it this morning, you said that in terms of distribution of digoxin in the body, after the transport system has done its work and carried the digoxin to various sites to which it will bind, that the tissues, certain tissues in any event, carry far greater concentrations of digoxin than are left in the blood. Is there any way, Doctor, to your knowledge or in your opinion in which digoxin which is bound to tissue may become unbound and reenter the bloodstream, other than in the case of the process of elimination, which you described this morning? May there be an otherwise, if you will, spontaneous loosening of that bond so as to elevate blood levels, reduce tissue levels?

A. Well, it's hard to know under what circumstances this may occur, but there are two where I think -- in fact, we have some information. One is the situation where an individual is put on an extra-corporeal pump situation, and I think that's a very esoteric situation, that is, where an individual undergoes open heart surgery is



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put on a pump to sustain the circulation while the heart is being examined. During those situations we have observed that wash out of digoxin from skeletal tissues to occur and there is an elevated concentration that we find in the post-pump period in these patients.

Now, that's an interesting point.

That's one very esoteric and highly unusual situation where that may occur.

Second possibility, and perhaps there are others, relate to the potential effects of other drugs on displacement of digoxin from its binding site, or binding sites, I think plural is probably more appropriate.

There have been in the past few years suggestions that the drug quinidine, which is used to alter the rhythm of the heart, it is what is called an anti-arhythmic. That would be a drug used to restore the rhythm of the heart to a normal rhythm. This drug is associated with abnormally elevated levels of digoxin in patients who are receiving both agents concurrently. Whether that has significance in cases under concern, I don't know. There may be other circumstances and other drugs that perhaps influence this measurement



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in a similar manner. There are some. Again, I can bring that to the proceedings, this information later.

Q. Thank you. Can we go on to another situation which you will have to tell me may cause tissue bound digoxin to become unbound. What about death? Is there any evidence that post-mortem, digoxin previously found in the tissue may become unbound and reenter the circulatory system?

A. Well, the problem is as follows. The binding of a drug to a receptor is very similar to the binding of digoxin to the antibody I showed in that figure. That binding is not an irreversible process. Though digoxin binds to something on the surface of the cell, the receptor, the receptor is a protein. Proteins undergo a variety of changes. When the cell dies the receptor undergoes degeneration and it is very conceivable and, in my opinion, very likely that the binding of digoxin to the tissue would be substantially altered.



FF
DM/PS

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2 My guess is that it would be sub-
3 stantially reduced. Consequently, if I were to
4 take that tissue and attempt to -- well, again
5 here it's a problem, visualize, if you can, the
6 death of an organism in which the digoxin has been
7 bound to the tissue. If one recovers those tissues
8 or a tissue, one day later, if the body has been
9 kept in a freezer it is conceivable that the tissue
10 might be quite satisfactory. Or, if the body has
11 been kept in an ice chest, not frozen, but cool,
12 that binding in that protein may not have been
13 denatured, undergone an autolytic process
14 extensively. However, after a period of time
15 mortification will set in and you will have destruction
16 of the proteins to which the digoxin is bound and
17 the digoxin would then dissociate and float into
18 whatever media was available.

17 So I think they are fraught with
18 all types of difficulties and problems that I can't
19 even begin to imagine at this juncture.

20 Q. Doctor, we have heard that
21 digoxin levels in blood drawn post-mortem may
22 be higher by a factor of 2, 3, or even 4 than the
23 levels that exist in that blood ante-mortem, is
24 that an observation that is consistent with your
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2 experience of reading of the literature?

3 A. Well, I must admit that I
4 didn't come adequately prepared to touch on that
5 point. I think that the issue is that if you have
6 the patient embalmed it is clear that some of the
7 embalming fluids would dissociate digoxin from
8 the tissues. I think that that is the situation
you are talking about.

9 Q. I'm not going that far down
10 the road.

11 A. Oh.

12 Q. I am talking, for example,
13 about blood drawn at autopsy.

14 A. Oh, at autopsy?

15 Q. Yes.

16 A. I think a lot of it will
17 depend on how soon after death, so to me that is
a point where the time parameter is very crucial.

18 There are circumstances where the
19 binding of the digoxin to the tissue probably would
20 be sustained for a finite period of time, assuming
21 the body was kept in the cold, as most of the time
they are.

22 Q. Yes.

23 A. If this was the case, then I
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2 think it was likely that even there the measurements
3 probably would be different. I think -- I can't
4 expect that the binding would be the same as it
5 would be under normal conditions where the blood
6 is being oxygenated, etc.

7 I think it is important to recognize
8 that another crucial factor that influences binding
9 is the PH and acidity of the blood, and when death
10 occurs the blood usually is extremely acidic and
11 this may have a very marked effect on loosening
12 the bond between digoxin and its protein binding
13 site. I don't have the data on that point
14 available to me.

15 Q. That brings us to one of the
16 last topics I wanted to deal with, Doctor, and
17 that is the question of post-mortem blood and
18 tissue samples. First, with respect to post-
19 mortem blood for the purpose of radioimmuno assay,
20 Can you tell us, is it important to know the site
21 from which a blood sample is drawn post-mortem?

22 A. Well, I think it probably will
23 be of some relevance. For example, if one takes,
24 as you know, each organ in the body has an artery
25 and a vein, the artery brings blood to the organ and
the vein takes it away. It would be my guess that



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2 blood drawn from the vein which is emanating
3 from an organ which contains a high concentration
4 of drug, since that is essentially the channel,
5 the conduit through which anything that was in
6 the organ would emerge, that the vein might have
7 a higher concentration than the artery in post-
mortem.

8 Q. Yes.

9 A. Now, a lot of this depends
10 on how the post-mortem is done and exactly where
11 the sample is taken from. Commonly samples may
12 be taken from the large veins leading into the
13 heart, I am not sure what site these were taken
14 in any patients.

15 Q. I'm not talking about
16 particular patients, I am just asking you generally
17 a site of the sampling in post-mortem blood.

18 A. I think that is an example
19 that might be of some consequence. Another
20 example would be if the blood were obtained from
21 a compartment that did not regularly equilibrate
22 with circulating blood. For example, blood is
23 known not to, certain drugs are known not to
24 establish rapid equilibrium, that is, do not
25 achieve the same concentration in the blood as they



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2 do in the tissue. For example, in the brain it
3 takes a longer time to achieve a concentration
4 in the brain for some drugs than it does, as I
5 say, the heart or the kidney. So, if one were
6 to take blood from the brain it would be a
7 question of whether or not this blood taken from
8 the brain adequately or adequately reflected the
9 concentration that was in the circulating blood
at the same time.

10 One overcomes this by making
11 comparisons between the so-called central circulation
12 and perhaps the peripheral circulation.

13 Q. Would it be important
14 for you, Doctor, to know the period and the manner
15 of storage of a post-mortem blood sample in order
16 to make a reliable interpretation of the RIA reading
of that sample?

17 A. Well, I was impressed that
18 the serum and/or plasma specimens are usually
19 fairly stable. Most of them are collected and kept
20 in the cold, put in the freezer and assayed
21 subsequently, some time later in the week, perhaps.
22 From my experience this is a way we handle all
23 our specimens, we kept them cold and put them away
24 in the freezer and would do them when the assay was
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2 available.

3 One could visualize the digoxin
4 breaking down if it were kept at room temperature,
5 or 37 degrees for too long a period, but I think this
6 compound is quite stable and I would not expect too
7 much breakdown, even if the specimens, even if the
8 blood specimens were not stored in the manner I
suggested.

9 Q. I take it from that that had
10 there been some unusual or anomalous manner of
11 storage, extended period of storage, that might
12 go to your ability to place reliance upon the
13 significance of the RIA reading. For example,
boiled, for example.

14 A. Pardon me?

15 Q. If a sample had been boiled
16 at some stage.

17 A. Yes, I see your point. Some
18 extreme mismanagement of the sample might introduce
19 an error.

20 Q. This, Doctor, may be an unfair
21 question and tell me if it is. I give you one piece
22 of information, that is to say that in a post-
23 mortem sample of blood drawn from a ventricle heart
24 blood, the RIA discloses a reading of, let us say
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60 nanograms per millilitre.

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THE COMMISSIONER: 60?

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Q. I plucked a number out of the air. Would you be able with that piece of information to form an estimate as to the dosage that produced that level; and/or as to the time of administration of that dose; and/or as to the method of administration of the dose? I picked 60 and it is a very low level. The thrust of my question is can you infer ante mortem events as to dosage times method of administration from a single post-mortem level?

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A. I think it is extremely difficult, and I suppose one would really have to know when the drug was given, I think that is a very crucial piece of information. If I knew when the drug was given and how, then I could make a guess, even from a single point that might be within reason as to how much was given. Shall I go on further?

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Q. Well, is it any two out of three, if you knew how much was given and how it was given, could you estimate when it was given?

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A. How much and --?

Q. And how.

A. How? Well, I think one could make an estimate, but that does create a problem. It



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2 creates a very severe problem. The reliability of
3 the estimate, I think, decreases precipitously with
4 the lack of each piece of information. Now, if I
5 may go on a bit.

6 Q. Yes.

7 A. If in this imaginary sequence
8 the drug was given intravenously, let us say, that
9 would be probably the easiest circumstance under
10 which we can make some very interesting, some
11 interesting conclusions. If the drug were given
12 intravenously and if we had the blood level measure-
ment, and if we knew how much was given.

13 Q. There wouldn't be much left
14 to answer, would there?

15 A. I could tell you when, I think
16 pretty easily with a margin of error, so I think we
need this data.

17 Q. Do I take it, Doctor, what
18 you are telling me is that you would need to have
19 considerably more information than merely a post-
20 mortem blood level in order to be able to say very
21 much about the size, time or method of administra-
22 tion of the dose which led to that level?
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A. Yes, I think that is it exactly, yes.

Q. Can we come to levels in tissues, Doctor? Are you able to by reference to recorded levels of digoxin in post mortem tissue, and let us focus on fresh post mortem tissue, are you able by reference to recorded levels in fresh post mortem tissue to draw any conclusion or any opinion as to whether those levels represent therapeutic or toxic loading with digoxin?

A. I would generally say that we could not reach any conclusion on that score.

Q. That strong. How strong could you reach - what is the difficulty about drawing such a conclusion?

A. First of all, we do not really have, in my opinion, critical information that will allow me to state unequivocally what constitutes a normal or acceptable concentration of the drug in given tissue under a given therapeutic situation.

Admittedly, there are data available which will show the concentration of drug in a piece of heart tissue taken from a patient who has received digoxin for a long period of time, and one can make some relationship between the serum concentration



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and the concentration of drug in that piece of heart tissue.

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That data has been established and various ratios have been suggested. In fact, I will give you some of those. It is a very wide range.

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From the paper I referred to earlier, in one study the average was a ratio of 104 to 1, that is the ratio of digoxin in heart tissue to plasma. So it is tissue to plasma concentration. The average was 104 to 1. Do you have that?

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Now, the range was extraordinarily large. It ranged from I think 47 to 1, to 174 to 1, so it was a very broad range and there are some other data here that suggest that the ratio, that ratio is much higher in younger children, it is in the order of 100 or 104 to 1, or 100 to 1, compared to adults where the ratio is 40 or 50 to 1. So it is stating that the heart tissue of younger infants take up more of the digoxin relative to a given plasma concentration than the adult. Do I have to go over that again?

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Q. No, I think I understand that.

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A. Now, until one really has a problem - has a data base that allows us to say with certainty that that is what would occur in all



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Q. A little under 2 in serum?

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individuals, only then I think can we take a given tissue level, perhaps, and maybe relate it back to a serum level. For example, this gets back to the question in some way that you asked earlier. Suppose I was dead certain that that 104 to 1 occurred in all patients - simple. I would take the serum level - or suppose we had a patient where we had a concentration of 200, let us say 200 in tissues, so I would assume --

A. Exactly. The problem of course with that simplistic analogy is we lack I think the information to reach such a lovely conclusion because this would enable us to take even a post mortem specimen, assuming all things being equal, that the post mortem specimen represented a valid measurement of digoxin in the tissue. If anything, at worst it would represent an underestimate and that is a nice paradigm, I think. The only thing missing is data, but that has never stopped us before, and I think we are really stymied at this juncture. It is a problem. I think that it is a problem that confronts us in analyzing information of this sort.

Q. But Doctor, you have told us earlier that although there may be wild anomalies



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both above and below any given range, people tend to think in terms of a range and to look closely at things that fall outside of it, because the range encompasses the norm, does it not?

A. I think that is a reasonable assumption.

Q. If, then, you were to establish that an average ratio of hard tissue concentration to serum levels was 140 to 1 and if you were to record a level of 1400 in the heart --

A. 1400?

Q. Yes.

A. Yes.

Q. Would that not suggest to you, on the average, the probability of a corresponding serum level which you would regard as likely falling in a toxic range, that is to say, 10?

A. I think that your logic is incontrovertible.

Q. I agree 140 may not be the magic number. There may not be a magic number. There may not even be a broad range?

A. The logic I say is valid, in my mind. The problem is, as I have tried to explain, is our difficulty with the initial proposition. I



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am sure you understand that.

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Q. I understand entirely.

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A. But I think the way of dealing with it seems to me acceptable in this theoretical framework, and the real question in our minds is how reliable is the estimate we are making? Is this 10 that we come up with, 10 plus or minus 20 which obviously would make it relatively invalid, or is it 10 plus or minus 1, and, if the latter is the case, then I think we may have evolved an approach to dealing with this data.

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I am not honestly sure that I know the answer to that. My understanding of it - contemporary understanding of the data available is that we cannot make that assumption with any certainty. My sense of this is that the error is much larger, that the standard error in that figure is very high, so that we could not make that determination with any degree of assurance. That is the problem; obviously.

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Q. Is not the irony of it this, though, Doctor. You told me earlier that the purpose of measuring serum levels in the live patient was to try to infer that loading in the tissues which would produce a therapeutic but not a toxic result. The irony is, as I understand you, that given the



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loading in the tissues you are still unable to say whether that represents therapeutic or toxic loading?

A. Yes. I think the reason probably is that we really are not sure what other factors are determining the entry of the drug into the tissue and it may be that drug may accumulate in the tissue. I hope I make this point clearly. The drug may accumulate in the tissue and yet not reflect the serum level in this direct relationship that we are postulating, but life is full of such ironies.

Q. After a time we become philosophical about it. I was talking, Doctor, about fresh autopsy tissue. I take it the difficulties you have outlined are in no way resolved. If we are talking about fixed autopsy tissue, are they?

Indeed, if anything they are magnified. The difficulties of making any assessment of whether a recorded level in fixed autopsy tissue represents toxic or therapeutic levels?

A. I think that is almost a hopeless case unless one can take the tissue, if the tissue was stored in a bottle of fixative. It usually is not, if we take it out of a patient whose body has been profused with embalming fluid. That is one



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circumstance, and one does not know how much of the drug has been leached off by the embalming fluid, and so I think that is a very difficult assessment.

One, on the other hand, if Mr. Lamek's question is phrased differently, if one took the tissue and had it placed in embalming fluid in a bottle one could then perhaps assay the embalmed fluid as well as the tissue and come up with a total content of the drug, provided that the drug had not been decomposed by the embalming fluid.

It is my understanding that there are some embalming fluids that indeed do cause decomposition of the drug. Now, that is hearsay. I don't have accurate documentation of that statement, but I gather it is true, and we can find that out.

Q. But even if you could do a total assay of the specimen of tissue plus the fixed fluid which has been stored, you would really be in a position, as if it were fresh autopsy tissue, with the difficulties that you have already outlined, as I understand you?

A. That is correct, so presumably the recommendation should be made that we get both plasma specimen and the autopsy tissue from the same patient if possible.



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Q. You said the last one was almost impossible. Were you able to draw any inference or conclusion as to toxic or therapeutic levels of digoxin from those recorded in exhumed tissue?

A. Exhumed tissue means tissue taken from a body after an indefinite period of time?

Q. Months of burial, yes.

A. I think I am really going here from intuitive sense. I would be very hard pressed to know what that meant. I would not accept those data at face value.

Q. What do you mean that you would not accept the data at face value?

A. That they reflect accurately the content of the tissue at the time of death.

Q. That they reflect accurately the content of the tissue or the concentration of the content of the tissue?

A. Well, let us get on to this.

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When we talk about concentration, we are talking about amounts of digoxin per unit weight of tissue.

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Q. Yes.

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A. Is that correct?

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Q. Yes.

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A. When we talk about total content,

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we are essentially taking the concentration and multiplying by the total weight of the organ available.

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Q. Yes, okay.

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A. Okay.

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Q. Okay, we are talking about the

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same thing.

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A. Are we, good.

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Now, I meant to say that merely

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because we measure something at a given point after death, that that does not allow me at least to

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conclude that that was the concentration of the drug

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at the time - that is the concentration of the drug

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in that tissue at the time of the patient's death.

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Q. Yes.

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A. For the reason I think we've

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discussed previously.

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Q. Yes.

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A. However, I think, as I think

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about this very carefully, if one does have an

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excessively high concentration in that tissue, just let us say that it is very, very high relative to what we've seen in our theoretical ratio, perhaps one might infer something from that relative to the serum concentration that existed at the time of death. Okay?

Q. Yes.

A. On the other hand, if the concentration is very low, I don't think we can conclude anything because it does not say that it was not high at the time of death.

Q. That's right.

A. For the reason we've discussed.

Q. Could you say at least this, Doctor. In the case of exhumed tissue that if levels of digoxin are recorded in exhumed tissue and they are levels of a sufficient elevation to persuade you that you are dealing with more than metabolites or digoxinlike endogenous substances or anything of that sort, substantial levels, could you at least say this, that those findings enable you to say that digoxin was present in the body at the time of death. Although you may not be able to say in what concentrations and what quantities?

A. I think that sounds reasonable to me.



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Q. Okay. Final topic if I may, Doctor. I said I would be through by 4 o'clock and I think I'm just going to make it. I just referred to possible digoxinlike endogenous substances and you have referred in the course of your testimony today on two or three occasions to recently published data apparently recording material which either reacts or cross-reacts with the digoxin antibody and the RIA in patients who had not received digoxin. The current thought as I understand it appears to be that there may be an endogenous digoxinlike substance with cross-reactivity in the RIA for digoxin.

Now, you are familiar with those reported studies, I take it?

A. Yes, I am.

Q. As I recall it, and we will hear tomorrow from one of the authors of one of those studies, Dr. Seccombe, his findings are at least were recorded in very young infants. You have said earlier today that there is a changing sensitivity to digoxin as a child progresses through the neonate into the infancy stage and beyond. Do you attach any significance to the findings being recorded in very young infants, in neonates?

A. I think these are in some ways



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2 pivotal to our discussion, particularly insofar as
3 the very young infant is concerned. If these findings
4 are substantiated, and it appears now that there may
5 be observations at two laboratories, that this then
6 raises questions about the assay as it is executed
7 in the plasma of infants, in the plasma obtained
8 from infants of this age group. For example, what
9 this does essentially is to falsely elevate a given
10 plasma concentration that would be discerned by the
11 radioimmunoassay. I hope that's clear. Because
12 what you are doing is, every assay starts with a
13 given, with a blank, so to speak, so that you carry
14 out the procedure in a specimen to be analyzed that
15 does not contain any of the material you wish to
16 assay, zero amount. This essentially tells you what
17 is the background in that particular specimen. Whether
18 there is cross-reactive material, whether there is
19 anything that would falsely elevate the reading.

20 Now, if you have plasma or specimen
21 that has something in it that cross-reacts with the
22 antibody, then you're going to get a spurious
23 elevation in the concentration of digoxin that you
24 assay with this technique.

25 As a consequence, therefore, it is
imperative that in assays carried out in very young



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infants at least, assuming that this material is only present in the young infant, the very young infant, in assays carried out in that population of patients, one, it is mandatory that you have a blank from the patient. That is a specimen of blood which is obtained prior to administration of the digoxin and rarely do you have it. It is as if we went around and took a blood specimen from everybody in a healthy state and put it in a bank and had that available for such circumstances as this.

So, I think it does throw into considerable question some of these assays and one would have to have the authors of this report perhaps specify for us wherever possible and in intimate detail what kind of contribution it actually makes. It could be that the contribution of this endogenous material is relatively low. In those circumstances it may not be a problem.

I was looking for the paper here. I have a copy of it with me.

Q. I have it too. Certainly one of the levels recorded was in excess of 4 nanograms per millilitre, which would be a very substantial contribution to an RIA review.

A. I think that's true. Certainly



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one which added on to what might be a normal, of something of two in a patient might cause someone to be quite concerned.

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On the other hand, it may be possible if this contribution is fairly constant again we can sort of subtract it out ad hoc. Now, I hesitate to suggest that. I'm sure the author of this report would be horrified at that suggestion, and I would also.

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So, I don't mean to take it lightly. I mean to emphasize the importance of this observation, if I may, and suggest that we look at it, you look at it very carefully to see how it may falsely elevate, have elevated some of these values.

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MR. LAMEK: Mr. Commissioner, it is a few minutes before four and a very odd time to suggest this, but I wonder if we could have a very brief break, perhaps for five minutes, I think I'm finished but I would like a word with Dr. Mirkin before I finally say that I am. Can we do that please, Mr. Commissioner.

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THE COMMISSIONER: Yes. We'll take five minutes.
--- Short recess.



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2 --- Upon Resuming

3 MR. LAMEK: Mr. Commissioner, for
4 this relief much thanks. Just a couple of small
5 matters that I would like to perhaps clarify with
6 Dr. Mirkin before I close.

7 Q. Dr. Mirkin, you referred
8 this afternoon to that hail and hearty child who
9 was admitted to your hospital, I think you said
10 after a single acute dose, overdose of digoxin
11 recording a serum level of, you recall, 50 to 55
12 nanograms per millilitre. I think you said he had
13 a healthy heart. Was he in any respect, as far as
14 you could see, unhealthy.

15 A. None.

16 Q. Okay. Not the sort of child
17 to whom digoxin would normally be administered in
18 any event, I take it?

19 A. No, that's correct. I only
20 use that case to illustrate a distinction in a normal
21 patient between those who received the drug chronically
22 obviously would not be given to a normal patient, and
23 an individual who suffered from an acute ingestion
24 of a large amount of a toxic agent. I use it to really
25 point out the importance of distinguishing between
26 these events.

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2 Q. Doctor, with respect to infant
3 cardiac patients, are you able to recall the highest
4 serum level that you have seen amongst such patients
5 who are receiving digoxin on a routine basis?

6 A. I think in patients who are
7 monitored quite carefully we have had patients who
8 have gone up to 8 or 10 nanograms per mill before
9 sometimes we are able to catch it.

10 Q. And were those patients
11 exhibiting any signs of toxicity?

12 A. The ones that I recall did
13 begin to show toxic signs, probably at about 10 and
14 there are probably some where we saw it at substantially
15 lower concentrations. These would be arthhmias
16 primarily.

17 Q. I asked you a number of
18 questions about post mortem levels of digoxin blood
19 and in tissue and the interpretation of those levels
20 if such interpretation was possible. I need to be
21 fair to you, I didn't mean not to be Doctor. Have you
22 in your clinical practice or in your reasearch ever
23 done any level assays in post mortem tissue or
24 interpreted assay results in post mortem tissues?

25 A. Well, I could be a bit more
26 specific. We have not carried out post mortem studies
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2 in human infant or adult tissue or biological specimen
3 but we have done, as I realise now, considerable
4 work in using animals in post mortem specimens.

5 Q. With respect to children in
6 your hospital, you are telling me that there is no
7 post mortem study which you have been involved?

8 A. None.

9 Q. All right. And fairly,
10 therefore, I take it your answers to me were based
11 upon your reading of such literature as there is on
12 that subject?

13 A. That's correct.

14 Q. I think there was one slide
15 you thought would be helpful to us, Doctor, in under-
16 standing something you have said. I wonder if we
17 could see that now, please.

18 A. Can you see this top one?
19 I have another copy of that which is larger if you hang
20 on a second. I'm sorry I can't do any better than
21 that. Well, bad news, I'll have to shout.

22 Q. You call and I'll point, how
23 is that?

24 A. Yes, stand up comics!. That's
25 fine, thank you

26 Now, the only point - there are two
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2 slides which I would like to show. This will show
3 the serum digoxin concentration and this is the
4 percentage of individuals who had intoxication.
5 These are adults not children.

6 First off, you will notice that here
7 we have concentrations, as I mentioned in the adult,
8 about 1.5 might be considered therapeutic. Here they
9 have it up to 2, but this is about right. You can
10 see that most of the patients in the open bars are
11 non-toxic. When we start getting concentrations that
12 exceed 2 and all the way up to greater than 8, you can
13 see then that there is an increasing frequency of
14 intoxicated patients. But the critical point that I
15 would like you to recognize is that there is an overlap
16 from 1.5 to 3, even in the adults.

17 Okay, that is a substantial number of
18 patients.

19 So, even in the adult, the cut off
20 point is not as precise as we would like it to be,
21 although, it seems like it is much better than it is
22 in childhood.

23 THE COMMISSIONER: You are going
24 to have to distinguish these various parts of
25 Exhibit 6 somewhat. I don't know how, but perhaps
26 you could read them into the record.

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Yes, I wonder if I could deal with them, Exhibits 6A, 6B and so on with a title for each and I am sure we can do that.

THE COMMISSIONER: Yes.

THE WITNESS: Now finally this is a slide that is taken from a paper that we published, this is on children. There are two points that I think I want to emphasize. First, this is a concentration which goes from zero up to 5.6 nanograms per millilitre and along this sets out the hours after administration.

I think it is a point to recognize that here is the controlled blood level in these patients before they received a dose. All these patients were on, were receiving a standard routine dosage of digoxin and their level in this calculation is in the young infants, 2.4 to, there was one very low down here. This is 12 hours after the last dose. The dose that was given here is zero hours and we measured it on an hourly basis, the blood level. The key here is this: that when a blood level is taken from a patient, when is an appropriate time to take it? Quite obviously if one were to take a specimen within an hour or two after an oral dose now, these are all doses here, one would get a relatively high



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concentration and yet it should be emphasized, even in these patients with concentrations of 5.6 to 5.2 up here, after one hour, we could not, we were unable to establish any meaningful correlations with toxicity.

So, therefore, if one were to try to relate that blood level to toxic events, you get into a very jumbled interpretation. We therefore, and I think others concur in this, felt that it was important to emphasize the time after administration of the dose at which the serum concentration should be measured, and on the average came out to something 5 or 6 hours. You can see from this, right about this point that it came down from the higher level beginning to plateau out in a more flat line. In that way I think one can be assured, at least better assured, that some of these concentrations may have some more relevant relationship as predictors. So again I think as we examine blood levels in greater detail it is important to pick on a time after drug administration at which the specimens were obtained.

MR. LAMEK: Q. Doctor, you just raised one point and I would like you to clarify it and it will only take one question.

You said you sampled, I think it was 12 hours after administration of the oral dose?



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A. That was the controlled specimen which we used. You see, these drugs are usually given every 12 hours.

Q. What is an appropriate period of time to permit to elapse between dosage and sampling?

A. I think I tried to emphasize between 5 and 6 hours which would give us, eliminate that post-absorption peak and allow an accurate reflection of what the serum level is after the drug is distributed.

MR. LAMEK: Doctor, thank you very much indeed.

Mr. Commissioner, it is 4:20, I think Dr. Mirkin deserves a short break before he meets with other Counsel, may we say 5 o'clock in the Commission's offices?

THE COMMISSIONER: All right, some of us will not be there.

MR. LAMEK: In Hearing Room No. 2 on the 21st floor, Mr. Commissioner.

THE COMMISSIONER: All right. Yes Mr. Marshall, what is your problem?

MR. MARSHALL: May I, Mr. Commissioner, when these charts and graphs are made available, may they also include the source from which those charts



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and graphs were obtained, what papers or textbooks,
or whatever, both the source and the date?

THE COMMISSIONER: Is that possible?

THE WITNESS: Certainly, I think it
is imperative.

THE COMMISSIONER: I think that will
be on the document itself. Those documents have not
yet been tendered and when they are tendered they will
have a letter after the 6 and some more precise
identification, so we can know when it should be and
perhaps we may even have to read it into the
transcript.

MR. LAMEK: I am content with that,
Mr. Chairman, as soon as they become documents that
is what I will do.

MR. MARSHALL: I have one other
problem.

THE COMMISSIONER: Yes.

MR. MARSHALL: I understand that today
was the date that the statement of facts, prima facie
facts was to be released for public mauling.

THE COMMISSIONER: I think it is going
to be tomorrow.

MR. MARSHALL: Will the various
responses that have been filed with Commission Counsel



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at that time then be filed as exhibits, sequential exhibits?

MS. CRONK: Mr. Commissioner, if I may, this morning the comments received from all other Counsel were circulated amongst other Counsel, it is our hope to at least make recommendations just as to how the statements should be treated, if not tomorrow, Thursday.

THE COMMISSIONER: We will deal with it further at that time. Nothing dreadful is happening overnight.

Those of us who are not going to meet at the Commission offices at 5 o'clock will meet here tomorrow at 10:00 a.m.

MR. MALEK: Thank you, sir.

THE COMMISSIONER: Dr. Mirkin, it has been a pleasure meeting you.

MR. ORTVED: Just as a point of procedure. I spoke with Mr. Lamek about this, now that we are getting to a large number of exhibits I wonder if it is possible to have distributed a list of exhibits so we are all dealing from the same basis.

THE COMMISSIONER: A list of numbers?

MR. ORTVED: Yes, but I think really you are looking at the wrong person, Mr. Elliott is



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II 6 2 the man to do that.

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4 --- Whereupon the hearing was adjourned at 4:25 p.m.
until Wednesday, June 29th, 1983 at 10:00 a.m.

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